# AUDIOLOGICAL PROFILE IN PRIMARY SJOGREN'S SYNDROME IN AN INDIAN SETTING

*DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE RULES AND REGULATIONS FOR THE M.S. BRANCH IV OTORHINOLARYNGOLOGY EXAMINATION OF THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY*

*TO BE HELD IN APRIL, 2012*


# AUDIOLOGICAL PROFILE IN PRIMARY SJOGREN'S SYNDROME IN AN INDIAN SETTING

SUBMITTED BY

**Dr. THANOOJA C. V.**

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE RULES AND REGULATIONS FOR THE M.S. BRANCH IV OTORHINOLARYNGOLOGY EXAMINATION OF THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

TO BE HELD IN APRIL, 2012

# Certificate

This is to certify that the dissertation entitled **"Audiological Profile In Primary Sjogren's Syndrome in an Indian Setting"** is the bonafide original work of Dr. Thanooja C.V submitted in fulfilment of the rules and regulations for the MS branch IV, ENT examination of the Tamil Nadu Dr. MGR University, to be held in April 2012.

**Guide and Head of the Department**

**Dr. Achamma Balraj**
Professor and Head
Audiovestibular Unit
Department of Otorhinolaryngology
Christian Medical College
Vellore, India

## Acknowledgements

First of all I thank God Almighty for strengthening and guiding me throughout the work and for sustaining me during difficult times.

I would like to express my deep gratitude to my Professor and Guide Dr. Achamma Balraj, Head of Department of ENT and Chief of Audiovestibular Unit, CMCH for all her encouragement , wisdom, patience and guidance throughout the work on my thesis.

I would like to thank my co-investigator Dr. Debashish Danda, Professor and Head of Department of Clinical Immunology and Rheumatology, CMCH for all his guidance, support and encouragement throughout the study.

I would like to thank Dr. Ann Mary Augustine my co investigator for all her support and help in carrying out the study.

I am grateful to all the doctors of Rheumatology department especially Dr. John Mathew and Dr. Sandhya for their immense help and support in doing this study.

I am extremely thankful to all the audiology lab staff for their constant support.

I wish to thank Mrs. Premalatha J, ENT 4 secretary for all her help and support throughout the study.

I am grateful to all the staff in Biostatistics department especially Mr. Prasanna, Mr. Sathiya Murthi and Microbiology and Biochemistry departments.

I am thankful to all the patients who consented to be a part of this study.

I would like to thank the Fluid Research Fund Committee for giving me the financial support to carry out the study.

I wish to thank my husband Dr. Vinod Joshua, with his support and timely help in crucial situations my thesis became a reality.

Last but not the least, I wish to thank my daughter Nivedita, for her smiling face which lifted up and encouraged my soul.

# TABLE OF CONTENTS

**Abstract:**

**Title: Audiological profile in Primary Sjogren's Syndrome in an Indian setting**

**Objectives**

This is a prospective study to determine the frequency and the profile of hearing loss among patients with confirmed diagnosis of primary Sjogren's Syndrome (pSS) in an Indian setting. Secondary objective is to analyse the correlation between hearing loss and immunological variables which includes Anti SS-A antibody, Anti SS-B antibody, Anticardiolipin, Complement C3, C4 and Cryoglobulins.

**Literature Review**

Sjogrens Syndrome is a cell mediated autoimmune disease which primarily affects the exocrine glands. The disease primarily affects women, with a very high female-male ratio of 9:1 and is seen in 40-60 years age group (1). Hearing loss may be the first otological manifestation of this autoimmune disease (1). Sensorineural hearing loss (SNHL) is found in half patients with pSS and is correlated with presence of anticardiolipin (ACA) antibodies (1)

Most studies done in the western countries ( 2,3,4,5) have shown that pSS is associated with significant sensorineural hearing loss(3). SNHL was found to be associated with disease duration, there was no correlation with age, presence of autoantibodies, systemic manifestations of disease, or drug therapy. Some of the studies (2,4) showed an association of hearing loss with immunological variables such as anti SS-A, anti SS-B, anti-phosholipid antibodies and anti-nuclear antibodies. This study is undertaken to see if the audiological profile is similar to the reported literature.

**Methodology**

All consecutive patients with established diagnosis of pSS as per the Modified American European Classification Criteria between 20-60 years attending at the Clinical Immunology and Rheumatology OPD of CMC Vellore were referred to the AudioVestibular clinic over a period of 10 months. These patients who fit into the inclusion, exclusion criteria underwent a history taking with detailed structured questionnaire and ENT examination, necessary audiological and blood tests. Frequency of hearing loss, its profile, relationship with immunological tests were analysed. All the data were entered into an excel sheet using Microsoft Excel and was analysed using SPSS version 11.0

**Results and Conclusions:**

The frequency of primary Sjogren's disease is high in this tertiary care rheumatology clinic in this Indian setting. The frequency of audiometrically confirmed hearing loss in pSS is 78.38 %. The commonest type of hearing loss was minimal to mild sensorineural hearing loss. The high frequencies were more affected than lower frequencies. The commonest tympanometry finding was A type curve . Acoustic reflex was absent in 18.92%. The frequency of hearing loss was found to be more in the 1$^{st}$ year after onset of SS than after 5 year duration. There seems to be no co-relation between hearing loss and age, sicca symptoms, systemic symptoms, immunological test results in pSS.

**Key words**: Primary sjogrens syndrome, hearing loss

**References:**

1.Harrison's practices of clinical medicine 2009

2.Boki KA,Ioannidis JP,Segas JV,Maragkoudakis PV,PetrouD,Adamopoulus GK,et al .How significant is sensorineural hearing loss in Sjogrens syndrome? J Rheumatology 2001;28:798-801

3.Ziavra N,Politi EN,Kastanioudakis,Shevas A,Drosos AA.Hearing loss in Sjogrens syndrome patients;a comparative study.Clin Exp.Rheumatology 2000 Nov-Dec;18:725-8

4.Tumaiti B,Casoli P,Parmeggiani A.Hearing loss in Sjogrens Syndrome.Ann Int med1997;126:450-3

5.Hatzopoulas S,Amoroso C,Aimoni C,Lo Monaco A,Govoni M,Martini A.Hearing loss evaluation of Sjogrens Syndrome using distortion product otoacoustic emissions .Acta otolaryngology suppl 2002;(548):20-5

6.Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann. Rheum. Dis. 2002 Jun;61(6):554–8.

# INTRODUCTION

Sjogren's syndrome is a common autoimmune disorder affecting 2–3% of the adult population (1). This cell mediated immune disorder is characterised by lymphocytic infiltration and destruction of the exocrine glands, especially the salivary and lacrimal glands, leading to dry mouth and dry eyes, the hallmark of the disease (1). Ear involvement is not uncommon in autoimmune diseases. But only few data on this problem in primary Sjogren's Syndrome (pSS) are available (2). If the autoimmune pathology is restricted to the ear, it is known as primary auto immune ear disease (AIED) and if multi systemic, organ non specific auto immune disease involve the inner ear, it is known as secondary AIED which includes Cogan's syndrome, Sjogrens syndrome (SS), Wegner's granulomatosis, systemic lupus erythematosus and various systemic vasculitides (3). Sensorineural hearing loss (SNHL) was commonly reported as the first otologic manifestation of autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus , polyarteritis nodosa and Wegener granulomatosis(4–8). Only very few studies have analysed hearing loss in pSS. Previous studies reported hearing loss in pSS, which was mainly SNHL; Tumaiti et al (2) reported hearing loss in 46%; Trott et al (9) reported 21.4%, Hatzopoulos (10) 36.3% and Ziavara et al (11) reported hearing loss in 22.5% patients. The pathogenesis of immune-mediated SNHL is still not clear. It includes immune complex mediated vasculitis in the inner ear (4) and auto antibodies directed against inner-ear antigenic epitopes (5). Boulassel et al found that 44% of patients with autoimmune hearing loss had auto antibodies directed against 30, 42 and 68 kDa inner ear proteins in sera. (12)

# AIMS AND OBJECTIVES OF THE STUDY

1) To determine the frequency and the profile of hearing loss among patients with confirmed diagnosis of primary Sjogren's Syndrome in an Indian setting.

2) Secondary objective is to analyse the correlation between hearing loss and immunological variables which includes Anti SS-A antibody, Anti SS-B antibody, Anticardiolipin, Complement C3, C4 and Cryoglobulins.

# PRESENT KNOWLEDGE AND REVIEW OF LITERATURE

Sjogren's Syndrome is systemic autoimmune disease which mainly affects the exocrine glands. It usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands. SS is a cell-mediated immune disorder. If there is no associated systemic autoimmune disease, patients with this condition are classified as having pSS (13). The spectrum of the disease includes an organ-specific autoimmune disease that is autoimmune exocrinopathy to a systemic process with multiple extraglandular manifestations(13).

Other exocrine glands, including those of the pancreas, bronchial tree and gastrointestinal tract may also be affected . The spectrum of clinical manifestations of pSS is very wide ranging from mucosal dryness, to more systemic complaints, affecting mainly the musculoskeletal, pulmonary, renal, neurological and vascular systems. Peripheral nervous system disease, manifests commonly as peripheral sensory neuropathy or more rarely as mononeuritis multiplex. (1)

## Prevalence

Among the two to four million persons in the United States having SS (14), one million have an established diagnosis. The disease remains undiagnosed in most cases because of the nonspecific nature of its clinical manifestations. The disease primarily affects women, with a very high female-male ratio of 9:1 (14). This could be because of the influence of sex hormones. Androgens has immune suppressor role, but oestrogens act as immune-stimulants. It may occur in patients of all ages (10), it affects patients in the fourth to sixth decades of life. Approximately 60% of SS patients have the disease secondary to an accompanying autoimmune disorder such as rheumatoid arthritis,

systemic lupus erythematosus, or systemic sclerosis (14). In a study by Fox et al (2000), it was seen that 500,000 to 2 million pSS patients in the United States have hearing loss (15). Since 1997, only very few studies have analysed hearing loss in pSS (2) . Hearing loss may be the first otological manifestation of this autoimmune disease . Ziavra N et al (11) found that 22.5% of pSS patients presented with SNHL of cochlear origin affecting mainly the high frequencies. This prevalence was lower than that found out by other investigators (2,10). SNHL was found to be associated with disease duration. A correlation between SNHL and the duration of the disease was found, while there was no correlation with age, systemic manifestations of the disease, presence of auto antibodies or drug therapy (10). Primary SS is associated with sensorineural hearing loss affecting mainly the high frequencies (2); but clinically significant defects are uncommon. Boki et al observed significant differences in hearing loss at 4000 Hz and 8000 Hz and minimal hearing loss affecting the lower frequencies. There was no evidence of retro cochlear pathology or increased vestibular involvement (16). Tumaiti et al reported sensorineural hearing loss in 46% of patients with pSS (2).

**Pathogenesis**

Chronic immune system stimulation is the basic pathophysiology of SS . The exact mechanism of the underlying humoral and cellular autoimmune reactions is unknown. Both T and B lymphocytes are involved. B cell hyper reactivity is manifested as hypergammaglobulinemia and circulating auto antibodies. Organ specific auto antibodies are produced against the cellular antigens seen in the salivary ducts, nerve cells, thyroid gland, erythrocytes, gastric mucosa, pancreas and the prostate. In approximately 60% of patients with SS non organ specific auto antibodies are found. These auto antibodies include antibodies to the small RNA protein complexes, which includes SS-A and SS-B,

rheumatoid factor and antinuclear antibodies. These auto antibodies contribute to tissue dysfunction before inflammation is evident (17).

Focal lymphocytic infiltrates around the glandular ducts including lymphocytic infiltration of the salivary and lacrimal glands and exocrine glands of the respiratory and gastrointestinal tracts and vagina is the histopathologic features in SS. The infiltrate contains T cells, B cells and plasma cells, with predominant activated $CD4^+$ helper T cells. T cells produce interleukin (IL)-2, 4, 6, 1, and tumor necrosis factor (TNF) α (18). 20% of the infiltrates consists of B cells. These locally produce immunoglobulins. These immunoglobulins have auto antibody reactivity (19). The infiltrate in the acinar epithelium, leads to glandular dysfunction which manifests as sicca features and enlarged major salivary glands (20).

The inflammatory processes of pSS occur mainly via glandular epithelial cells. These cells express antigen presenting proteins. These cells can promote adhesion, and co-stimulate T lymphocytes. The antigen-presenting function of epithelial cells is enhanced by cytokines like interferon IFN -γ and TNF-α. IFN-γ induces apoptosis of salivary gland epithelial cells (SGECs). This is by up-regulation of the Fas protein. Fas protein is a cell surface receptor. Its activation leads to apoptosis (21). The expression of CD40 protein is high in cells of patients with SS. CD40 can also be induced in SGECs by IFN-γ and IL-1β (22). SGECs have important role in the induction of lymphocytic infiltrates in patients with SS (14).

**Immune mediated hearing loss**

Auto immune ear disease (AIED) was defined by McCabe as a rapidly progressive bilateral SNHL that responds to the administration of immunosuppressive

agents (23). The concept of autoimmune hearing loss was first described by Lehnhardt in 1958 (24). He described an antigen antibody reaction in the hearing organs which improved with steroids. If the pathology is restricted to the ear, it is known as primary AIED and if multi systemic, organ non specific auto immune disease involve the inner ear, it is known as secondary AIED which includes Cogan's syndrome, Sjogrens syndrome, Wegner's granulomatosis, systemic lupus erythematosus and various systemic vasculitides (3).

**Pathogenesis of immune mediated hearing loss**

The pathogenesis of immune-mediated sensorineural hearing loss is not clear. It includes immune complex mediated vasculitis in the inner ear (4) and auto antibodies directed against inner-ear antigenic epitopes (5). Boulassel et al reported that antibodies to myelin P0 and beta-actin proteins can be seen in the serum of patients with auto immune ear disease. Abnormal expression of these proteins will lead to cellular-signal transduction dysfunction leading to various vestibule auditory complications (12). Anticardiolipin antibodies may be associated with sudden SNHL in patients with autoimmune diseases (25). Tumiati et al reported that anticardiolipin antibodies may be responsible for SNHL in the pSS (2). Tumaiti et al in their study found that 90% of pSS had antibodies to SS-A and 66% had antibodies to SS-B. All patients with the pSS who had SNHL had antibodies to SS-A positive. 64% patients who had SNHL had anticardiolipin antibodies compared with 18% patients in the normal hearing group (2). A high prevalence of cranial neuropathies resulting from the pSS was generally recognized. The symptoms and signs of eighth-nerve disorder in pSS have not been specifically sought(26).

Ziavara et al had reported SNHL in all the 22.5% patients with hearing loss in pSS. All of them had SNHL of cochlear origin (11). Boki et al had reported that none of their pSS patents had retrocochlear pathology (16). The deposition of immune complexes is considered to be the cause for high prevalence of cranial neuropathy in pSS (2,12,27) The deposition of immune complexes in the stria vascularis or in the endolymphatic sac via complement activation can cause endolymphatic hydrops leading to vestibular symptoms(16).

In Boulassel et al study on patients with autoimmune hearing loss, 44% of the patient's sera had autoantibodies directed against many inner ear proteins. Of these the 30, 42 and 68 kDa inner ear proteins were found to be the most reactive. Further studies had shown that the 30 and 42 kDa inner ear proteins being the major peripheral myelin protein P0 and the beta-actin protein, respectively. Sequence analysis showed that the 68 kDa protein is novel. The study findings supported the hypothesis that several populations of antibodies contribute to the enhanced immunological activity of AIED (12). Previous studies had demonstrated that, 58 kDa protein being extracted from guinea pig or bovine inner ear tissue, is the target of antibodies in serum samples from patients with AIED.

In another study by Boulassel et al, it was confirmed that the 58 kDa inner ear protein is the COCH5B2 protein. After separating inner ear proteins by gel electrophoresis and studying, it was found that the sequence of amino acids in the first to third fragments were identical to the amino acids 526 to 539, 417 to 427 and 396 to 405 of the COCH5B2 protein. Target protein 58 kDa antibodies in serum samples of AIED patients is the COCH5B2 protein. This molecule is highly and specifically expressed in the cochlea and vestibule (28).

Harris et al using a sterile labyrinthitis showed that inner ear is not an immune privileged site (29,30). Inner ear can generate local immune response after local or systemic immunisation of the antigen. Through the spiral modiolar vein, cells that mediate labyrinthitis enter the scala tympani. Resulting labyrinthitis cause physiologic dysfunction, loss of sensory cells ultimately leading to fibrosis and osteogenesis in the cochlea.

The guinea pig model shed light on the specific antibody that binds to 68-kD bovine inner ear antigen. This antibody was found in human with AIED and it binds to the inducible form of bovine heat shock protein 70 (HSP-70) (31). The primary antigenic epitope of this antibody and its role in AIED is unclear.

Nair et al found KHRI-3 a particular antibody, which binds to the supporting cells of organ of Corti, 68 to 72- kD antigen of inner ear extract. There was strong evidence that KHRI-3 antibody , and human antibodies can recognize the same inner ear supporting cell antigen (32,33).

Recent data shows that KHRI-3 targets multiple peptides similar to those seen in the highly conserved protein CTL2 which is abundantly expressed in inner ear (33). CTL2 coprecipitates with cochlin , which is one of the most expressed inner ear protein. As cochlin has critical role in maintaining the structure and function of inner ear, mutation can cause cochleovestibulopathy. Cochlin specific serum antibody was elevated in AIED patients.

Animal model study of multisystemic organ nonspecific autoimmune disease showed the increase in auditory thresholds, degeneration of stria vascularis, and the deposition of antibodies in the strial capillaries without any inflammatory response. The

etiology of strial degeneration is unknown (34–36). The studies on reversal of hearing loss on glucocorticoid and mineralocorticoid administration suggest that alteration of local ion transport in the cochlea can revert the hearing loss (37).

Studies showed that morphologic changes seen in human temporal bones of patients with autoimmune disease is consistent with 2 different pathogenic mechanisms. Some bones showed fibrosis and osteogenesis in the scalae indicating the end stage of inflammation. Other bones showed cellular atrophy in the absence of inflammation which is suggestive of ischemia. A nonspecific vasculopathy with occlusion of labyrinthine artery without vascular inflammation and necrosis was seen in case of ischemia (34,36)

## Autoimmune antibodies

### Anti SS-A and Anti SS-B antibodies

Auto antibodies in the pSS are primarily directed against the Sjogrens autoantigens SS-A and SS-B and against IgG rheumatoid factor. The SS-A and SS-B autoantigens are composed of a number of antigenic proteins which are coupled to small RNA molecules. These RNA-protein particles are present in all human cells. These autoantibodies can be detected using counter-immunoelectrophoresis, immunoblotting technique, ELISA or RNA precipitation assays. Anti-SS-A antibodies are best detected with counter-immunoelectrophoresis .The preferred method of screening for anti SS-B antibodies in human sera is immunoblotting technique. Anti SS-A antibodies are found in 60-70 percentage of patients with SS. But anti SS-A antibodies are not specific markers for this disease (38). Anti SS-B antibodies are present in approximately 40 - 50 percentage of patients with pSS. Anti SS-B antibodies are more specific than anti SS-A antibody (38). The only other disease where the antibody can be detected is systemic

lupus erythematosus (15% positive). The possible pathogenetic role and origin of auto antibodies in pSS is still not clear. The auto antibodies may be the product of an oligoclonal B-cell proliferation.

Auto antibodies to nuclear antigens in patients with multisystem autoimmune disease like pSS are classified into two major groups; auto antibodies to DNA and non DNA antigens. The non DNA antigens include antinuclear antibodies to the extractable or soluble nuclear antigens. Soluble nuclear antigens are ribonucleoproteins (RNPs) which consist of small ribonucleic acid (RNA) molecules attached to non-histone proteins. There are three main categories: the U group including U1–U6 small nuclear RNAs, the Ro group and the La group. The Ro/SSA antigen is formed of a small nucleocytoplasmic RNA protein complex consisting of a 60 kDa protein. 60 kDa protein is associated with one of the four human cytoplasmic RNAs (hY1, hY3, hY4, hY5)(39–41).The La/SSB antigen consists of a 48-kDa protein and serves as a termination factor for RNA polymerase III(42,43).

The role of both Ro/SSA and La/SSB specific auto antibodies in the pathogenesis of pSS is still not clear. The presence of these auto antibodies in serum is associated, with earlier disease onset and longer disease duration and extraglandular disease manifestations like splenomegaly, lymphadenopathy, vasculitis, purpura, lymphocytic infiltration of labial salivary glands and recurrent parotid gland enlargement(44–47). Pourmand et al had reported a weak correlation between the serum titres of IgA antibodies and SS-A and SS-B antigens and oral and ocular sicca symptoms (48). Toker et al reported that serum titre of anti SS-A and anti SS-B is correlated positively with dry eye symptoms and negatively with tear production and he suggested the possible contribution of these autoantibodies to the pathogenesis of exocrinopathy in SS (49).

**Anti-cardiolipin antibodies** (ACA)

ACA are a form of anti-mitochondrial antibody directed against cardiolipin. It is found in several diseases including antiphospholipid syndrome, Behcet's syndrome, systemic lupus erythematosus (SLE), syphilis, livedoid vasculitis, vertebrobasilar insufficiency and idiopathic spontaneous abortion (50–52).

Anticardiolipin antibodies can be detected using an enzyme linked immunosorbent assay (ELISA) immunological test. It screens for the presence of $\beta_2$ glycoprotein1 dependent anticardiolipin antibodies (ACA).

**Complements**

Complement proteins are serum enzyme systems which help to mediate inflammation. It helps or "complements" the ability of phagocytic cells and antibodies to clear pathogens from body. It is part of the immune system known as the innate immune system which is not adaptable and it does not change over the course of an individual's lifetime. It can be recruited and then brought into action by the adaptive immune system(53).

More than 25 proteins and protein fragments make up the complement system, which includes serum proteins, serosal proteins, and cell membrane receptors etc. The test to evaluate entire complement system is known as CH50. The most commonly measured complement components are C3 and C4. The measurement of complement helps to monitor the disease over time. Complements normally circulate as inactive precursors (pro-proteins). Complement proteins are activated by immunologic events on interaction with immune complexes. When stimulated by triggers, proteases in the system cleave to

specific proteins and cytokines are released to initiate an amplifying cascade of further cleavages. The end result is activation of the cell killing membrane attack complex (53).

The basic functions of the complements are opsonization (enhancing phagocytosis of antigens), chemotaxis (attracting macrophages and neutrophils), Lysis (rupturing membranes of foreign cells) and clumping of antigen-bearing agents. The complement system play a role in many diseases with an immune component, like asthma, lupus erythematosus, glomerulonephritis, various forms of arthritis, autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, and rejection of transplanted organs(54,55). Deficiencies of the terminal pathway can predispose to both autoimmune diseases and infections. Low C4 level is seen in vasulitis associated with pSS. Vasculitis in pSS presents with purpura in the lower legs, low complement(C4) level, and cryoglobulin in the blood. Deposition of immune complex on the vessel wall cause destruction of vessel wall leading to complement activation and low complement level in blood (56)

**Cryoglobulins**

Cryoglobulins are immunoglobulins which precipitate in vitro at temperatures less than 37°C. It can produce organ damage through two different pathways . By vascular sludging, mainly in type I cryoglobulinaemia and immune-mediated mechanisms in mixed cryoglobulinaemia. Cryoglobulinaemia is associated with many illnesses like infections, autoimmune disorders, and malignancies (57) .

Manel Ramos-Casals et al reported cryoglobulins in the sera of (16%) of patients with pSS. Of these most were IgMκ monoclonal and IgG polyclonal. It was seen that

leukocytoclastic cutaneous vasculitis, HCV infection and hypocomplementemia are associated with the presence of cryoglobulins in the sera of with pSS patients (58).

Tzioufas in his study found that 17.4% of the patients with pSS had mixed monoclonal cryoglobulinemia during the first evaluation. There was a significant correlation between the presence of mixed monoclonal cryoglobulinemia and a higher prevalence of autoantibodies to SS-A and SS-B, and the extraglandular manifestations (59).

## Clinical Features

SS is an autoimmune disease associated with organ specific and systemic autoimmunity. Autoimmune thyroid disease was found in 45% of a series of patients with pSS (60). Vascular involvement in these patients result in peripheral neuropathy, gastrointestinal lesions and glomerulonephritis (61). Numerous systemic manifestations of pSS can contribute to difficulty of diagnosis.

### Fatigue

Severe debilitating fatigue may occur in 50% of patients with pSS. Patients do not feel refreshed on waking up (62). The cause of this fatigue is undetermined. Subclinical hypothyroidism frequently associated with pSS may contribute to the fatigue. Twenty two percentage of patients with primary SS will have fibromyalgia(63).

### Musculoskeletal Involvement

Primary SS is often confused with RA clinically. Intermittent polyarticular arthropathy of small joints is seen in pSS. At times it may be asymmetrical. Joint

deformity and mild erosions may occur. A non erosive arthritis, resembling that of SLE, may occur transiently (64). Arthralgias exist in approximately 53% of patients and myalgias in 22% of patients with pSS (65).

**Dermatologic Involvement**

Dry skin, skin rashes, burning skin, typical hypersensitivity rash, ulcerative lesions, violaceous discoloration of digits, Raynaud phenomenon are the dermatological manifestations in SS. Dry skin was found to affect 55% of pSS patients. A study reported 9 of 70 patients with pSS developed vasculitis involving small or medium-sized vessels; of these 8 had involvement of the skin (61). These dermatological findings are differentiated from those of SLE and scleroderma. Mild Raynaud phenomenon may be seen in 30% of patients with pSS (14).

A few patients may have severe pSS, which lead to the development of vasculitis and lymphoma in later life. Vasculitis presents with purpura in the lower legs, low complement (C4) level, and cryoglobulin in the blood. Deposition of immune complex on the vessel wall cause destruction of vessel wall leading to complement activation and low complement level in blood (56).

**Pulmonary Involvement**

Even though common, pulmonary involvement is not clinically significant in patients with pSS. Xerotrachea causes cough, which is the main respiratory symptom. Lymphocytic alveolitis, interstitial pneumonitis pseudolymphoma and fibrosis are other potential pulmonary complications. Up to 30% of patients may have subclinical pulmonary disease (66). Pulmonary function test may show small-airway obstruction.

**Gastroenterologic Involvement**

SS patients may have involvement of entire gastrointestinal tract. Malabsorption is caused by lymphocytic infiltrates of the intestine. Esophageal dysmotility has been reported in 36% to 90% of patients (67,68). Routine laboratory testing may show mild pancreatitis and hepatitis. It should be differentiated from hepatitis C and autoimmune hepatitis. Hepatic involvement is seen in about 7% of patients. There will be antimitochondrial antibodies and abnormal liver enzyme levels. The histopathologic appearance is comparable to that of early primary biliary cirrhosis (69).

**Renal Involvement**

Patients with pSS may have tubulointerstitial involvement of the kidneys like distal renal tubular acidosis, hypercalcinuria, or proximal tubule defects (70–72). Pathologic examination shows tubulointerstitial nephritis. Hematuria, proteinuria, and renal insufficiency may be manifested in patients who show evidence of glomerular lesions. Some of them may progress to nephrotic syndrome. Patients may develop renal vasculitis with hypertension and renal insufficiency (14).

**Neurologic Involvement**

Neurologic disease is one of the common significant systemic manifestations of pSS. It can involve both cranial and peripheral nerves and also the central nervous system. An increased prevalence of cranial neuropathies is a consequence of the pSS. Symptoms and signs of eighth-nerve disorder have been reported in some of the patients (26). Most physicians who regularly treat pSS patients may not routinely ask them about hearing loss or test them for audiologically detectable hearing loss (2). In one study, it was found that

22% (10/46) had peripheral neuropathy and it was the presenting clinical feature in 5 patients (11%). The neuropathy was associated with alterations of the endoneurial microvessels. Necrotizing vasculitis was not seen (73). Central nervous system involvement is very rare and its incidence is controversial(1). It was reported that, 14 (46%) out of 30 patients with pSS had sensorineural hearing loss and it was significant in 5 and the hearing loss was correlated with the presence of anticardiolipin antibodies, which is suggestive of an underlying autoimmune cause (2)

## Diagnosis of SS

### Clinical Signs and Symptoms

The spectrum of clinical manifestations of pSS is very broad and many symptoms of pSS are nonspecific. SS is seen more in middle-aged women. So the oral, cutaneous and vaginal dryness may initially be attributed to menopause. The sicca symptoms of eyes and mouth may be confused with anxiety and atopic symptoms. Xerostomia symptoms are mainly subjective and are common to many conditions (14).

Signs of lymphoproliferation include enlargement of the salivary glands, splenomegaly, lymphadenopathy, and lung infiltrates. Monitoring of laboratory parameters in these patients may reveal signs of the development of lymphoma. This includes leukopenia, anemia, appearance of monoclonal protein, and loss of specific autoantibodies (14).

## Characteristic Clinical Findings

In a study, stepwise analysis of individual symptoms in 169 patients with SS and 44 controls found that the combined sicca symptoms of mouth, eyes and sore mouth classified 93% of patients with pSS and 97.7% of control subjects (65).

## Ocular Manifestations

Dry eye is the most important ocular manifestation of pSS. Dry eye symptoms manifest as itching, grittiness, or soreness with a normal appearance of eye. Ocular complaints also include photosensitivity, eye fatigue, erythema, eye discharge, decreased visual acuity and the feeling of a film in the visual field (65).

Decreased tear film and abnormal mucus component cause accumulation of thick, rope like secretions along the inner canthus. Small superficial corneal epithelial erosions, filamentary keratitis, conjunctivitis due to Staphylococcus aureus infection are the ocular manifestations. Ocular complications include corneal ulceration, opacification, vascularization, and perforation (14).

## Oral Manifestations

Even though presenting symptoms of pSS are those of xerostomia, patient may not complain of oral dryness. Patient may complain of an unpleas ant taste, crackers, soreness, difficulty in eating or problems in controlling dentures (74). As the disease progresses, there will not be the normal pooling of saliva in the floor of the mouth. Oral mucosa become glazed, form fine wrinkles, tongue becomes red and lobulated, with complete depapillation, tongue stick to the palate causing clicking quality in speech (14).

Chronic salivary gland inflammation leading to decreased salivary flow can cause dental caries (75–77). Salivary glands produce 1 to 1.5 L of saliva per day. Saliva contains many antimicrobial factors which inhibit bacteria and fungi and salivary glycoproteins inhibit microbial attachment to oral epithelium (78–80). Saliva provides a continuous flushing system which keeps the mouth clean preventing bacterial colonization. So patients with SS can have an increased risk of periodontal disease, dental caries, and acute bacterial (staphylococcal or pneumococcal) sialadenitis. Other oral symptoms include soreness, fissuring of tongue, angular cheilitis, candidiasis, accumulation of plaque, adherence of food to buccal surfaces, and dysphagia (14).

**Additional Xeroses**

Desiccation of the vagina and vulva cause dyspareunia and pruritus (65). Decreased glandular secretions of the respiratory tract lead to dryness of nose, throat, and trachea resulting in persistent hoarseness and chronic, nonproductive cough. Decreased secretion from the exocrine glands of skin leads to skin dryness. Vasculitis in the skin manifests as purpura or urticaria. It may be associated with presence of anti SS-A antibodies and other systemic manifestations. The most common histologic finding is leukocytoclastic vasculitis which is necrotizing neutrophilic inflammation of dermal blood vessels, resulting in palpable purpura, with raised hemorrhagic skin lesions (14).

**Importance of Diagnostic Accuracy**

An early, accurate diagnosis of pSS can prevent or ensure timely treatment of many of the complications of the disease, recognition and treatment of systemic complications like interstitial lung disease and malignant lymphoma. A correct diagnosis

of pSS depends on recognition of the clinical manifestations, excluding differential diagnoses, and differentiating primary from secondary SS (14).

**Diagnostic Criteria**

Minor salivary gland biopsy has been considered the "gold standard" for the diagnosis of SS. Newer criteria allows classification of SS even without performing lip biopsy. American-European Consensus Committee modified and reapproved the criteria. It has almost 95% sensitivity and specificity for SS. These criteria include presence of subjective and objective sicca features, antibodies to autoantigens SS-A and SS-B, and also the characteristic histopathologic findings in minor salivary glands.

Modified European Classification criteria assist early and accurate diagnosis of SS

**Modified American European classification criteria for Sjogrens syndrome** (81).

I. Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's I test, performed without anaesthesia (≤5 mm in 5 minutes)
2. Rose Bengal score or other ocular dye score (≥4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (≤1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Revised rules for classification

**For primary SS** (81)

In patients without any potentially associated disease, pSS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of pSS, as long as either item IV (Histopathology) or VI (Serology) is positive

b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)

**Diagnostic Methods**

Assessment of the oral, ocular involvement is essential for the accurate diagnosis of SS. Schirmer's test for eye quantitatively measures tear formation by placement of a filter paper in the lower conjunctival fornix. The result is positive when <5 mm of filter paper is wet after 5 minutes. Rose bengal scoring test involves after placement of 25 mL of the rose bengal solution into the inferior fornix of each eye, the patient has to blink twice. Slitlamp examination can detect the destroyed conjunctival epithelium. The rose bengal score, which is the sum of the scores for damage found seen in 3 regions of the eye, is calculated. This score can define the presence of keratoconjunctivitis sicca (14).

Sialometry is the measurement of unstimulated salivary flow into the tube with calibration for 15 minutes. If the flow is > 1.5 mL, it is considered to be normal. It is simple and noninvasive. But this test alone cannot distinguish between the causes of xerostomia. Other tests to evaluate salivary gland involvement are parotid sialography and scintigraphy of the salivary gland. Gross distortion of pattern of parotid ductules and marked retention of contrast medium on sialogram is seen in patients with SS. Reduced

uptake as well as release of technetium Tc 99m pertechnetate, according to degree of xerostomia and salivary flow rate are the scintigraphic findings in patients with SS (14)

Minor salivary gland biopsy is a very specific test for assessing the salivary component of pSS. After the procedure patient will have temporary soreness, and there will be fast healing without much scarring. Focal lymphocytic sialadenitis is a characteristic histopathologic feature of SS. It is defined as multiple, dense aggregates of more than 1 focus ( 50 lymphocytes) in the perivascular area or periductal area in the most of sampled glands (14).

Serologic and laboratory findings in SS include diffuse hypergammaglobulinemia seen in 80% of patients. These autoantibodies include the immunoglobulins, rheumatoid factors, antibodies to the SS-A and SS-B and antinuclear antibodies. Anti SS-A is not specific for pSS. Cryoglobulins are present in about 20% of patients with pSS, which consist of monoclonal IgM $\kappa$ cryoprecipitable immunoglobulins with rheumatoid factor activity(82)

**The cytoskeleton of the organ of Corti**

The understanding of pathology of cochlea requires information on the morphology of the inner ear. The cytoplasm of the cells contain a filamentous network forming cytoskeleton. These intermediate filaments are proteins forming the basic elements of mammalian cells. They measure 7-14 nm in diameter. There are 5 classes of intermediate filaments. These are cytokeratins , desmin filaments, glial filaments, neurofilaments and vimentin filaments (83)

Immunohistochemical methods revealed the cytoskeleton ,innervations and neuronal structures of organ of Corti. All the supporting elements of the organ of Corti had cytokeratin including 5,8,18, and 19. These were expressed by the phalangeal processes and by their apical processes of inner and outer pillar cells, but not by Deiters' cell bodies and hair cells. A gradient of increased cytokeratin expression was seen from the base to apex of cochlea. Only marginal (epithelial) cells expressed cytokeratin in the stria vascularis, and it was uniform in all the coils of cochlea(83).

**Histopathology of organ of Corti in autoimmune hearing loss**

In guinea pig studies, it was seen that there were lymphocytic and polymorpho nuclear infiltrates in the scala tympani in inital period, later thickening of and cellular infiltration of round window membrane. This experimental auto immune labyrinthitis had remission after 4 weeks. There was evidence for the passage of antibodies from middle ear into perilymph. Harris and Ryan suggested endolymphatic sac as the possible source of antibody producing cells and of immunoglobulins. Harris et al also suggested that inner ear has got immunological functions including autoimmunity (83).

**Hearing Loss**

Organic causes of hearing loss can be classified into conductive and sensorineural. Sensorineural can be either sensory or neural. Neural cause is again divided into peripheral which is caused by any lesion of $8^{th}$ nerve and central which is caused by involvement of the central pathways (84).

**Conductive hearing loss**

Any disease process which interferes with the conduction of sound to reach cochlea causes conductive hearing loss . The lesion may be in the external ear, tympanic membrane, middle ear or ossicles upto the stapediovestibular joint, or eustachian tube dysfunction. Audiometry characteristics include lower frequencies being affected more, bone conduction better than air conduction with an air bone gap which is not more than 60dB (84)

**Sensorineural hearing loss (SNHL)**

This results from lesions of the cochlea, 8th nerve or central auditory pathways. When lesion involves cochlea it is known as sensory type, when the $8^{th}$ nerve is involved it is known as retrocochlear and when the lesion involves central auditory pathways, it is known as central deafness. The audiometric characteristics include hearing loss involving higher frequencies, no air bone gap, hearing loss which may exceed 60dB (84)

**Mixed hearing loss**

Elements of both conductive and sensorineural deafness are present in the same ear. There is air bone gap indicating conductive element and impairment of bone conduction indicating sensorineural loss (84).

## Degree of hearing loss

Different classifications exist for the degree of hearing loss.

**Classification of hearing impairment severity** (85)

This scale is the modification of Goodman (1965) by Clark (1981)

Degree of hearing loss

| | | |
|---|---|---|
| -10 -15dB | - | Normal hearing |
| 16-25dB | - | Slight (minimal) hearing loss |
| 26-40dB | - | Mild hearing loss |
| 41-55dB | - | Moderate hearing loss |
| 56-70dB | - | Moderately severe hearing loss |
| 71-90dB | - | Severe hearing loss |
| >90dB | - | Profound hearing loss |

95% of population has thresholds between -10 and +10dB hearing level

As the threshold for hearing increases the ability to understand speech decreases.

## Audiometric tests to assess hearing

Hearing of an individual can be assessed by various clinical and audiometric tests.

### 1. Pure tone audiometry

Audiometer is an electronic device which produces pure tones. The intensity of pure tones can be increased or decreased in 5dB steps. The air conduction and bone conduction audiometry is done to determine degree and type of the hearing loss. The modified Hughson-Westlake technique can be used for estimating the thresholds (85). Air conduction thresholds are usually measured for tones of 125,250, 500, 1K, 2K, 4K and 8K Hz and bone conduction thresholds for 250, 500, 1K, 2K and 4 KHz .The amount of intensity which has to be raised above normal level is the measure of the degree of hearing impairment at that particular frequency. The thresholds are charted in the form of a graph known as audiogram. The various degrees of hearing loss were calculated as average of the thresholds at 3 frequencies 500,1K and 2K Hz. These 3 frequencies are considered to be the most important for understanding speech and therefore the most important in estimating the degree of handicap which a particular degree of hearing loss can cause (85). The thresholds of bone conduction is a measure of cochlear function. The difference between the thresholds for air conduction and bone conduction thresholds is known as air bone gap, which is a measure of conductive deafness. Audiometer is calibrated in such a way that the hearing of a normal person, both for air and bone conduction is at zero dB, and there is no air bone gap. When the difference in air conduction thresholds between both ears is more than 40dB or above, the better ear is

masked by employing a narrow band noise to the non test ear to avoid getting a shadow curve from the non test ear (86).

**2. Impedance audiometry**

It is an objective test consisting of 2 components

1) Tympanometry
2) Acoustic reflex measurements

**Tympanometry**

When sound strikes the tympanic membrane, a proportion of the sound energy is absorbed and the rest is reflected. A stiffer tympanic membrane reflects more of sound energy than a compliant one. By changing pressures in the sealed external auditory canal and then measuring the reflected sound energy, the compliance and stiffness of the tympano ossicular system and thus the health or diseased status of the middle ear can be assessed. The first classification system of tympanograms described by Liden (1969) ,was modified by Jerger et al (1972), which became the most popular descriptive system being used now (86).

The equipment consists of a probe with 3 channels which snugly fits into external auditory canal. Channel1 delivers a tone of 220Hz, Channel 2 picks up the reflected sound through a microphone and Channel 3 brings about changes in air pressure in the ear

canal from positive to normal and then to negative. The compliance of tympano ossicular system is plotted against various pressure changes in the external ear canal .The different types of graphs obtained are called tympanograms which are diagnostic of certain middle ear pathologies (86).

**Jerger –Liden classification of tympanogram**(86)

Type A-normal tympanogram

Type As-Compliance is lower at or near ambient pressure. Seen in fixation of ossicles eg; otosclerosis, malleus fixation

Type Ad- High compliance at or near ambient pressure. Seen in ossicular discontinuity or thin and lax tympanic membrane.

Type B-Flat or dome shaped graph. No change in compliance with pressure changes, seen in middle ear fluid or a thick tympanic membrane.

Type C-Maximum compliance at negative pressure in excess of 100 mm of water. Seen in retracted in tympanic membrane and may show some fluid in middle ear. (86)

**Acoustic reflex**

A loud sound, 70-100 dB above the threshold of hearing of a particular ear, causes contraction of stapedial muscles which can be detected by tympanometry. Tone can be delivered to one ear and the reflex picked up from same ear or contralateral ear, called as ipsilateral or contralateral reflexes.

The reflex arc involved in ipsilateral reflex-$8^{th}$ nerve→ventral cochlear nucleus→ $7^{th}$ nerve nucleus →ipsilateral stapedius muscle.

The reflex arc involved in contrateral reflex- $8^{th}$ nerve→ventral cochlear nucleus→contralateral medial superior olivary nucleus→ contralateral $7^{th}$ nerve nucleus →contralateral stapedius muscle. The presence of stapedial reflex at lower intensities, eg.40 to 60 dB than the usual 70dB indicates recruitment and thus a cochlear type of hearing loss.

If a sustained tone of 500 or 1000Hz, is delivered 10 dB above acoustic reflex threshold, for a period of 10 seconds, it brings the reflex amplitude to 50%. This abnormal adaptation is known as stapedial reflex decay and is indicative of $8^{th}$ nerve lesion.

If ipsilateral reflex is present and contralateral reflex is absent, lesion is in the area of crossed pathways in brainstem (87).

# MATERIALS AND METHODS

**Study Design**: Prospective case series

**Study population**

This study was conducted over a period of 10 months (January 2011 to October 2011) in the Immunology and Rheumatology clinic and AudioVestibular clinic of ENT Department of the Christian Medical College & Hospital (CMCH), Vellore. All consecutive patients with confirmed diagnosis of pSS as per the Modified American European Classification Criteria, between age 20-60 years, attending the Clinical Immunology and Rheumatology OPD of CMC Vellore were selected for the study over a period of 10 months. All patients with established diagnosis of pSS who satisfied the inclusion and exclusion criteria were included in the study.

**Inclusion criteria**

1) Patients with confirmed diagnosis of pSS as per the Modified American European Classification Criteria
2) Age between 20-60 yrs

**Exclusion criteria**

Anyone with a past history of ear disease which are known to cause permanent sensory or conductive hearing loss like

1) Chronic suppurative otitis media
2) History of intake of ototoxic drugs like aminoglycosides and loop diuretics

3) History of head injury

4) History of ear trauma

5) History of ear surgery

6) Otosclerosis

7) Past history of exposure to loud noise

**Informed consent**

Informed consent was obtained from all patients included in the study. The consent form is attached as Appendix 2. Institutional Research Board (IRB) approval was obtained from the institution for the conduct of the study (IRB Min .No.7288 dated 22.9.10.)

**METHODS**

All consecutive patients with confirmed diagnosis of pSS as per the Modified American European Classification Criteria between 20-60 years attending at the Clinical Immunology and Rheumatology OPD of CMC Vellore were referred to the AudioVestibular clinic over a period of 10 months. None of them met the criteria for any other connective tissue disease. These patients with established diagnosis of pSS who fit into the inclusion, exclusion criteria underwent a history taking with detailed structured questionnaire and ENT examination. The patients then underwent necessary audiological and blood tests.

**Audiological investigations included**

Pure tone audiometry

Impedance audiometry.

The audiological tests were done in the audiology lab. (Colour plates)

**Blood investigations included**

Anti SS-A antibody

Anti SS-B antibody

Anticardiolipin (ACA)

Complement C3, C4 and

Cryoglobulins

Anti SS-A antibody, Anti SS-B antibody and Anticardiolipin tests were done in the microbiology lab by ELISA technique and serum Complement C3, C4 were done in microbiology lab by nephelometry and dilution method. Cryoglobulins were done in biochemistry lab with a fasting blood sample by manual qualitative analysis. Anti SS-A <20Ru/ml, anti SS-B <20Ru/ml, ACA <12units/ml, C3 90-180mg/dl, C4 10-40mg/dl values were considered in the normal range.

**Pure Tone Audiometry**

This was done in the acoustically treated sound proof two rooms setting. The pure tone audiogram was done using a properly calibrated GSI- 61 clinical audiometer to establish hearing loss. The air conduction and bone conduction audiometry was done to determine degree and type of the hearing loss. The various degrees of hearing loss were calculated as average of the thresholds at 3 frequencies 500,1K and 2K Hz. These 3 frequencies are considered to be the most important for understanding speech and therefore the most important in estimating the degree of handicap which a particular degree of hearing loss can cause. The modified Hughson-Westlake technique was used for estimating the thresholds (85).

**Air conduction testing:**

The head phone was placed over the opening of the external auditory canal. The ears are tested individually and the better ear is tested first. A series of frequency specific pure tones were presented through the ear phones. Patient was asked to respond each time he hears the sound stimulus. The audiologist calculated the auditory threshold which is defined as the lowest intensity level at which a patient can hear the tone at least 50% of the time. The threshold is obtained in dB at regular steps of 1000, 2000, 4000, 8000, 500 and 250 Hz. The results obtained are plotted on the audiogram sheet.

**Bone conduction testing:**

The bone conduction vibrator is placed on the mastoid process individually and hearing thresholds are obtained at various frequencies. The threshold is obtained in dB at regular steps of 1000, 2000 and 4000, 500 and 250 Hz.

**Impedance audiometry**

This includes tympanometry and acoustic reflex testing. The machine used in our lab is calibrated GSI Tympstar middle ear analyser impedance audiometer. The headset contains an ear phone to be placed on the ear and a probe which is to be inserted snugly into the ear canal according to the size of the ear canal. The probe delivers both a sound signal tone and changes air pressure towards the tympanic membrane and the middle ear system. The probe also picks up the changes in the compliance and delivers those changes outwards for recording.

A pure tone stimulus of 500-4000Hz at 70-100 dB above the pure tone hearing threshold is delivered through the ear probe. The stimulus is increased or decreased until acoustic reflex threshold is obtained which is reported in dB. For ipsilateral acoustic reflex testing, the pure tone is delivered through the probe and muscle contraction is recorded in the same ear. For contralateral reflex testing, sound is delivered through head phone and muscle contraction is recorded in other ear by a probe placed in it.

**ANALYSIS**

All the data contained in the proforma were entered into an excel sheet using Microsoft Excel. Continuous variables like age were summarised using means with standard deviations. Categorical variables were described using frequencies with percentages. Association between hearing loss and other categorical variables were assessed using Chi-Square test. The data was analysed using SPSS version 11.0

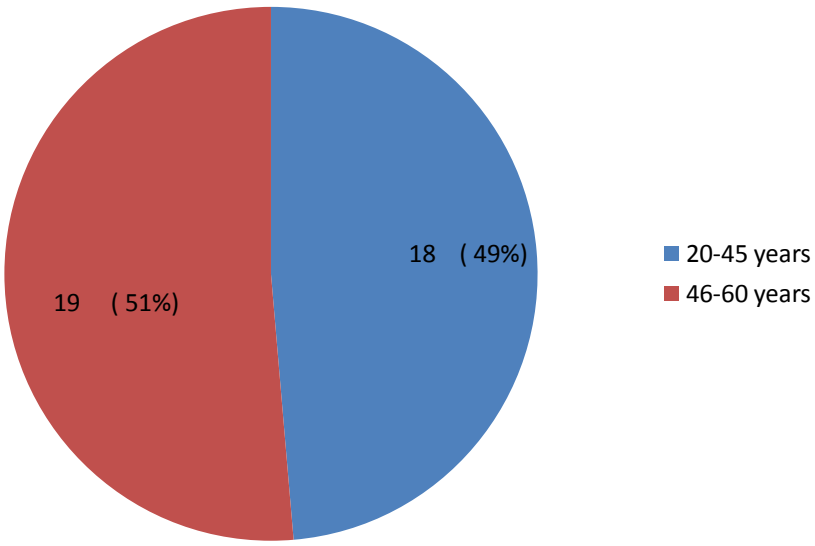
# RESULTS

There were 37 patients who were recruited for the study after applying the inclusion and exclusion criteria.

Figure 1 shows the age distribution.

The patients were between the age of 20-60 years; 18 were between 20-45 years, 19 were between 46 - 60 years. The mean age of the study group was 45 years; 36 were females and one was a male who was 37 year old.

**Figure 1 : Age distribution of 37 patients**



**Clinical presentation**

Table 1 shows the frequency of systemic symptoms patients presented with to the clinic:

Of the 37 patients, 34 (91.89%) had sicca symptoms; dryness of eye and mouth. The mean duration of sicca symptoms were 24 months with a minimum of 12 months and maximum of 180 months. The one male patient in the study group had sicca symptoms for 10 years.

Nineteen (51.35%) complained of foreign body sensation in the eyes. The mean duration of the eye symptoms was 24 months, with a range of 6 to 72 months. Of the 37 patients, 3 (8.11%) had recurrent enlargement of bilateral parotid salivary glands, 18 (48.65%) complained of multiple joint pains, with a mean duration 48 months.

**Table 1**

Systemic symptoms among the 37 patients

| Systemic symptoms | Present | Percent |
|---|---|---|
| Dry eye | 34 | 91.89 |
| Dry mouth | 34 | 91.89 |
| Recurrent enlargement of parotids | 3 | 8.11 |
| Multiple joint pain | 18 | 48.65 |

- Each patient had more than one symptom

The audiovestibular symptoms the patients presented with are shown in Table 2. Of the 37 patients, 5 (13.51%) complained of hearing loss. Of these 3 (8.11%) had unilateral hearing loss and 2 (5.41%) had bilateral hearing loss.

Five (13.51%) patients complained of tinnitus. Of these 4 (10.81%) had unilateral and 1(2.7%) bilateral tinnitus. The 5 patients who complained of hearing loss did not have tinnitus and the 5 who complained of tinnitus did not have hearing loss.

Three out of 37 patients (8.11%) complained of vertigo. Of these 2 had surrounding rotatory vertigo and 1 had light-headedness.

**Table 2: Audiovestibular symptoms among 37 pateints**

| **Audiovestibular symptoms** | **Present** | **Percentage** |
|---|---|---|
| Hearing loss | 5 | 13.51 |
| Tinnitus | 5 | 13.51 |
| Vertigo | 3 | 8.11 |

- Each patient had more than one audiovestibular symptom

Among the 37 patients, 34 (91.89%) were on treatment with Hydroxychoroquine (HCQ) and 18 (48.65%) on Methotrexate (MTX). The mean duration of HCQ treatment was 15 months (range 2 to 84 months). The mean duration of MTX treatment was 16 months (range 3 to 60 months).

The co morbidities of the patients are shown in Table 3.

Six (16.22%) had hypertension, 8 (21.62%) had hypothyroidism and 1(2.7%) had dyslipiidemia. None were diabetic.

**Table 3 Comorbidities among 37 patients**

| Co morbidity | Number | Percentage |
|---|---|---|
| Hypertension | 6 | 16.22 |
| Dyslipidemia | 1 | 2.7 |
| Hypothyroidism | 8 | 21.62 |
| Diabetes Mellitus | 0 | 0 |

Of the 37 patients, 28 had Schirmers test done. Of these, 27 (96.43%) patients had a positive Schirmers test confirming dry eyes; 1(3.57%) patient had negative Schirmers Test; in 9 patients Schirmers could not be done.

Table 4 shows the lip biopsy results. Of the 30 patients who underwent lip biopsy, 15 (50%) had a grade 4, 14(46.67%) had grade 3 and 1 (3.33%) grade 1 inflammation. The only one male patient in our study group had grade 4 inflammation. For 7 (18.92%) Lip Biopsy was not done.

**Table 4 Lip biopsy result in 30 patients**

| Test | Grade 4 | Grade 3 | Grade1 | Total |
|---|---|---|---|---|
| Lip biopsy | 15 ( 50% ) | 14 (46.67 %) | 1 (3.33%) | 30 (100%) |

Figure 2 and 3 shows the pure tone audiogram results of the 37 patients in the study.

29 out of 37 (78.38%) were found to have hearing loss on audiometry. Of these 37 patients, 24 (64.85%) had minimal, 4 (10.8%) had mild, and 1 (2.7%) had moderate hearing loss. 8(21.62%) patients had normal hearing on audiometry.

Among the 29, 28 had sensorineural and 1 had mixed hearing loss which was of moderate severity.

Of the 29 patients 24 (82.76%) had bilateral and 5(17.24%) unilateral hearing loss. The only one male patient in this study group had bilateral minimal SNHL.

**Figure 2: Pure Tone Audiogram result in 37 patients**

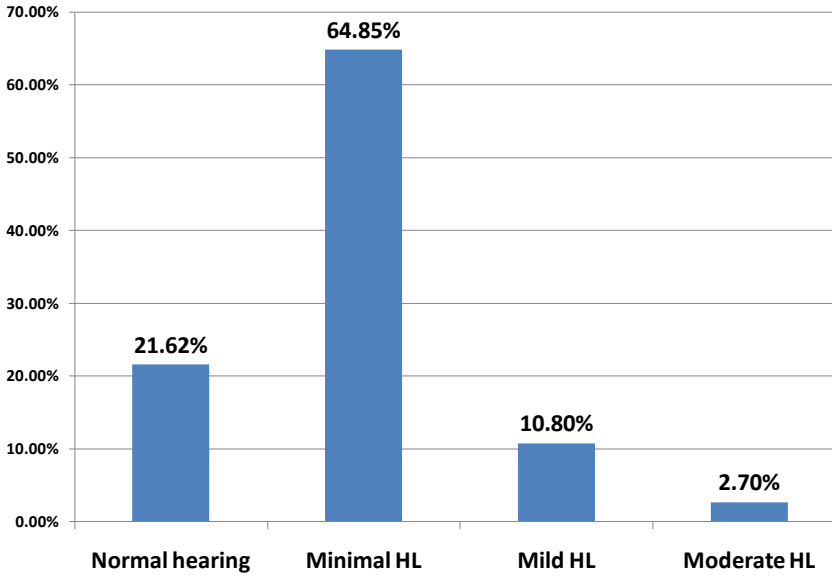
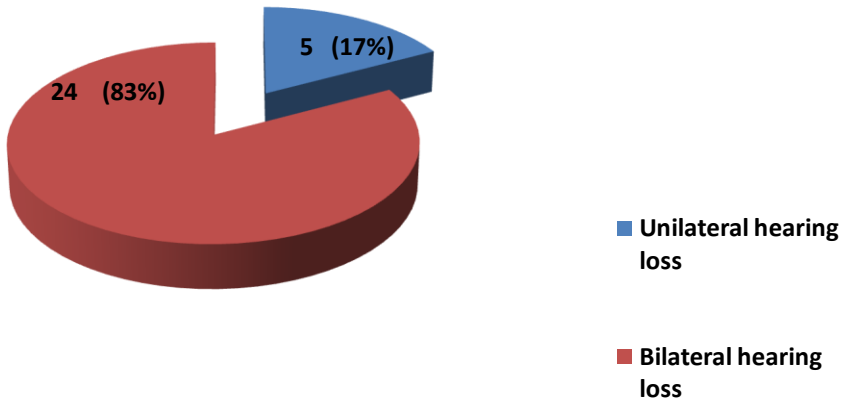



**Figure 3: Documented hearing loss among 29 patients**



Out of the 29 patients with hearing loss, 27 patients had a hearing loss affecting high frequencies 4KHz and 8KHz. The average threshold for the high frequencies was 28.56 dB with a maximum value of 82.5 dB.

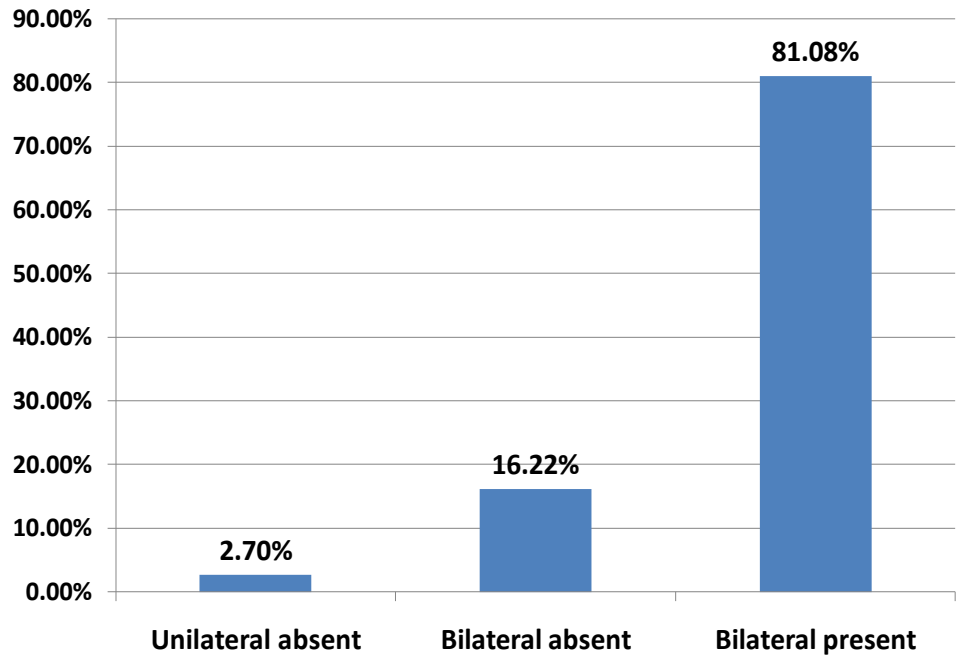
Table 5 and Figure 4 show the results of Impedance testing and acoustic reflex testing in the study group respectively. The commonest type of tympanogram was A type, found in 83.78% of patients.

**Table 5: Impedance audiogram results in 37 patients**

| Side | A | As | Ad | B | C | Total |
|---|---|---|---|---|---|---|
| Right | 31(83.78%) | 2 (5.4%) | 3 (8.11%) | 0 | 1(2.7%) | 37(100%) |
| Left | 31(83.78%) | 3 (8.11%) | 0 | 2(5.4%) | 1(2.7%) | 37(100%) |

Acoustic reflexes were absent in 18.92% patients.

**Figure4: Acoustic Reflexes in37patients**




Blood test results are shown in Table 6. Anti SS-A and anti SS-B tests were done in 35 patients and ACA was done in 31 patients. Of the 35 patients, 23(65.71%) had positive anti SS-A, 12(34.29%) had positive anti SS-B. Of the 31 patients, 2 (6.45%) had positive ACA titre.

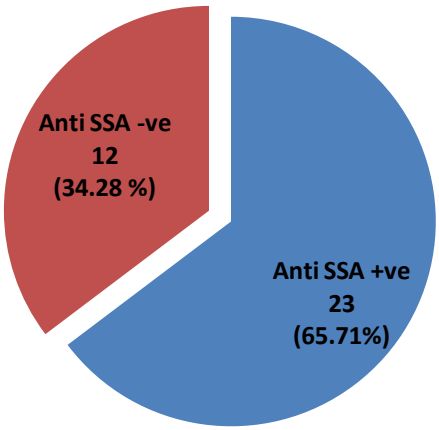
**Table 7 Blood test results**

| Tests | Positive | Negative | Total | Not done |
|---|---|---|---|---|
| Anti SS-A | 23(65.71%) | 12(34.29%) | 35(100%) | 2(5.4%) |
| Anti SS-B | 12(34.29%) | 23(65.71%) | 35(100%) | 2(5.4%) |
| ACA | 2(6.45%) | 29(93.55 %) | 31(100%) | 6(16.22%) |

Anti SS-A and anti SS-B antibody result shown in Figure 5A and 5B

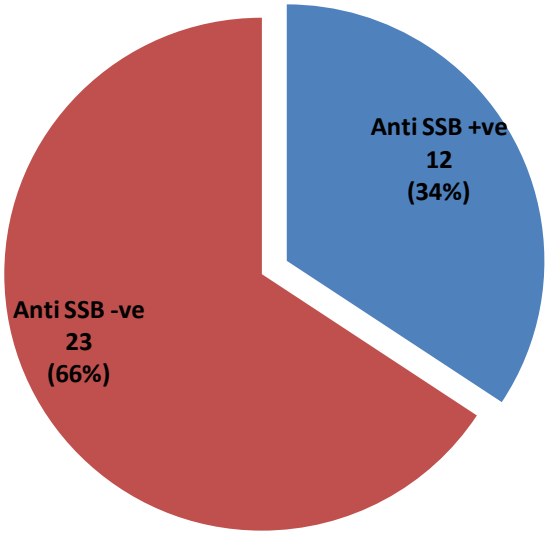
Of the 35 patients who had anti SSA test done, 23(65.71%) had anti SS-A positive (> 20Ru/ml), 12(34.28%) had negative titres. The mean titre value of anti SS-A was 98.8 Ru/ml.

**Figure 5A : Anti SS-A antibody in 35 patients**



Of the 35 patients who had anti SS-B test done, 12 ( 34.29 %) had a positive titre (>20Ru/ml) and 23 (65.71%) had a negative titre. Two patients did not have the tests done. The mean anti SS-B titre was 68.51Ru/ml.

**Figure :5B Anti SS-B antibody in 35 patients**



Of the 31 patients who had anticardiolipin antibody test done, 2(6.45%) had a positive titre (>12 units/ml) and 29(93.55%) had a negative titre. For 6 patients the test could not be done. The mean ACA antibody titre was 3.76 units/ml.

Serum C3 and C4 results are shown in Table 7

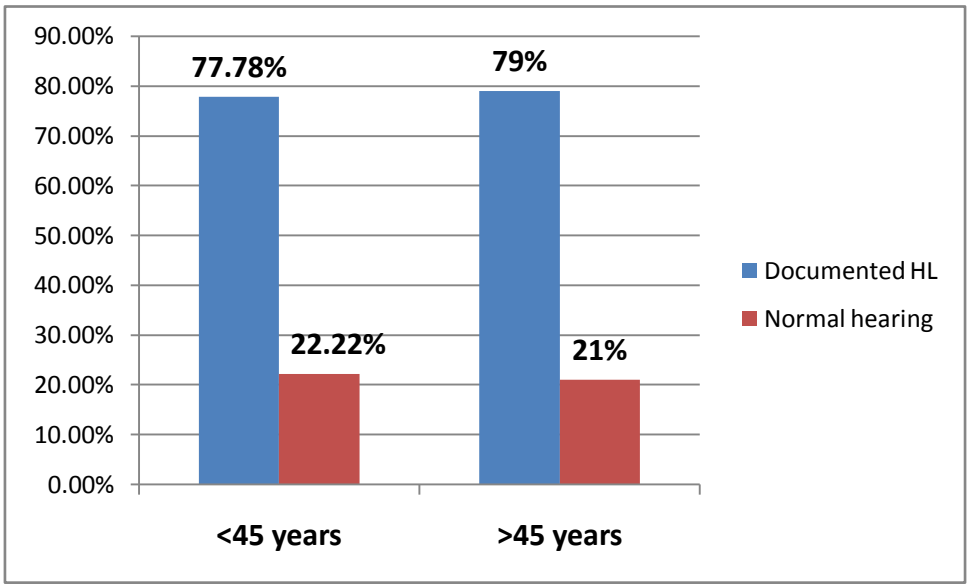
Of the 34 patients who had this test done, 33 (97.06%) had a normal C3 (90-180mg/dl) and 30(88.23%) had a normal C4 (10-40mg/dl) level in the serum. Only 1 patient (2.94%) had a low C3, C4 level, 3(8.82%) had a high C4 level and none had a high C3 level.

**Table 8 Serum Complements C3 and C4 test results among 34 patients**

| Test | Low | Normal | High | Total |
|---|---|---|---|---|
| C3 | 1(2.94%) | 33(97.06 %) | 0 | 34(100%) |
| C4 | 1(2.94%) | 30 (88.23%) | 3(8.82%) | 34(100%) |

Comparison between hearing loss and age group is shown in Figure 6. There were no differences in hearing loss between the age groups 20-45 and 46- 60 years (Chi sq 0.0075, P value = 0.935)

**Figure 6 Comparison between hearing loss and age group among 37 patients**




Out of the 34 patients with sicca symptoms, 27 (79.41%) had documented hearing loss and of the 3 patients without sicca symptoms, 2 (66.67%) had hearing loss; this difference was not significant (Chi sq 0.2642, P value - 0.607).

Out of the 18 patients who had multiple joint pains, 12(66.67%) had documented hearing loss and of the rest 19 without the symptom, 17 (89.47%) had hearing loss.

Out of the 34 patients who had complained of sicca symptoms, 27(79.41%) had documented hearing loss. Out of the 5 patients with sicca symptoms of >5 years duration, all of them had documented hearing loss.

Out of the 16 patients with dry eye of 1-5 year duration, 11( 68.75 %) had documented hearing loss and of the 18 patients with dry mouth of 1-5 year duration, 13 ( 72.22 %) had documented hearing loss.

Out of the 13 patients with dry eye of < 1 year duration, 11 ( 84.62 %) and of the 11 patients with dry mouth of < 1 year duration ,9 ( 81.82 %) had documented hearing loss .

There was no significant difference between healing loss with sicca symptoms for different duration (Chi square 2.6240, P value = 0.269 and Chi sq 1.9043 ,P value=0.386 for comparison with dry eye and dry mouth respectively)

Out of the 9 patients with Foreign body sensation of eye of < 1 year duration, 8 (88.89%) had documented hearing loss.

Of the 9 with same symptom of 1-5 year duration, 5 (55.56 %) had documented hearing loss and the only 1 patient who had the symptom of >5 year duration had documented hearing loss. This difference in hearing loss between patients with different duration of the symptom was not statistically significant. ( Chi sq 2.9556, P=0.228)

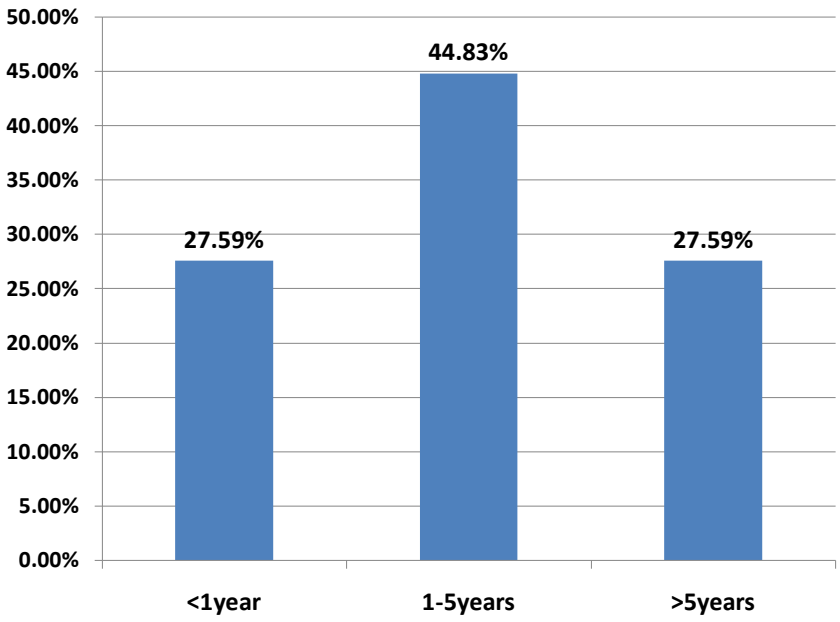
The results of comparison between the duration since the onset of disease and presence of hearing loss are shown in Figure 7.

Out of the 11 patients who had the duration of first symptom of SS for more than 5 years, 8(72.73%) had documented hearing loss.

Out of the 17 patients who had the duration of first symptom of SS between 1-5 years, 13 (76.47 %) had documented hearing loss.

Out of the 9 patients who had the duration of first symptom of SS of less than 1 year, 8 (88.89 %) had documented hearing loss. This difference in hearing hearing loss between patients with different duration of disease was not found to be statistically different. (Chi sq 0.8305, P=0.660)

**Figure 7 Comparison between the duration since the onset of disease and presence of hearing loss in 29 patients with documented hearing loss.**

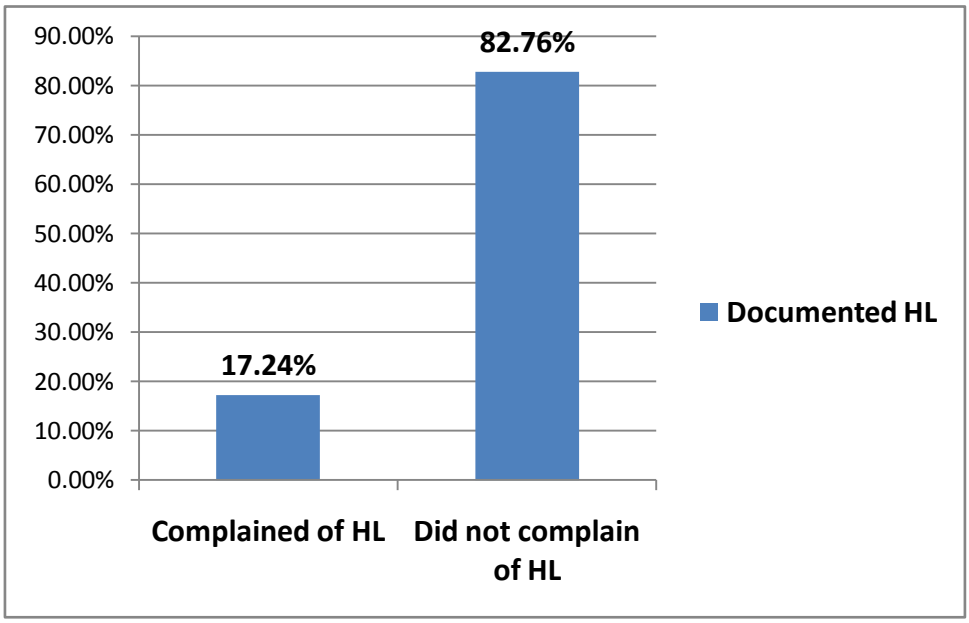



The comparison between audiometry proven hearing loss and hearing loss symptom are shown in Figure 8.

Out of the 29 patients with documented hearing loss, only 5(17.24%) patients complained of a decreased hearing. Rest 24(82.76%) were not aware that they had

decreased hearing. All the 5 patients who complained of a decreased hearing had a documented hearing loss.

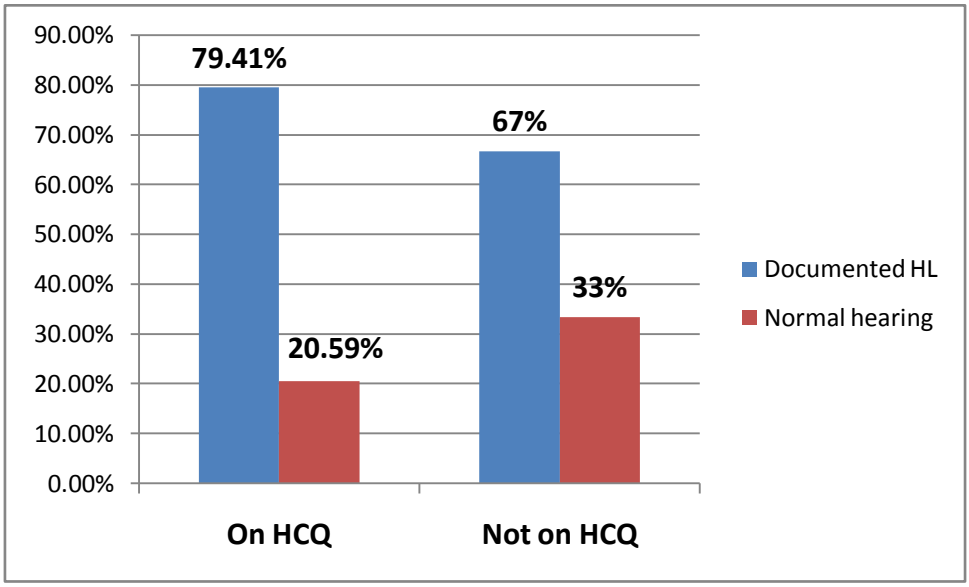
**Figure 8 Comparison between audiometry proven hearing loss and hearing loss symptom among 29 with documented hearing loss.**



Comparison between hearing loss and treatment with HCQ is shown in Figure 9

Out of 34 patients on HCQ, 27 (79.41%) had hearing loss on audiometry and of the rest 3 who were not on HCQ, 2 (66.67%) had hearing loss. This difference in hearing loss between patients on treatment and not on treatment with HCQ was not significantly different (Chi sq 0.2642, P = 0.607)

**Figure 9 Comparison between hearing loss and treatment with HCQ among 37 patients**



Out of the 4 patients who were on HCQ for more than 5 years, 3(75%) had documented hearing loss.

Out of the 13 patients who were on HCQ for a period between 1-5 years, 10(76.92%) had documented hearing loss .

Out of the 17 who were on HCQ for less than 1 year, 14(82.35%) had documented hearing loss. The difference in hearing loss between patients on HCQ for difeerent duration was not significantly different.(Chi sq 0.1868, P value = 0.911)

Of the 18 patients who were on MTX, 12 (66.67 %) had documented hearing loss. Out of the 19 who were not on MTX, 17 (89.47 %) had documented hearing loss.

The only one patient on MTX for more than 5 years had documented hearing loss.

Out of the 8 patients on MTX for a period between 1-5 years, 4 (62.5%) had documented hearing loss. Out of 9 patients on MTX for less than 1 year duration, 6 (66.67%) had documented hearing loss. This difference in hearing loss between patients on HCQ for different duration was not found to be significantly different. (Chi sq 0.5625, P value 0.755, was statistically not significant. Same issue here

Out of the 15 patients with a grade 4 lip biopsy, 10 (66.67%) had documented hearing loss.

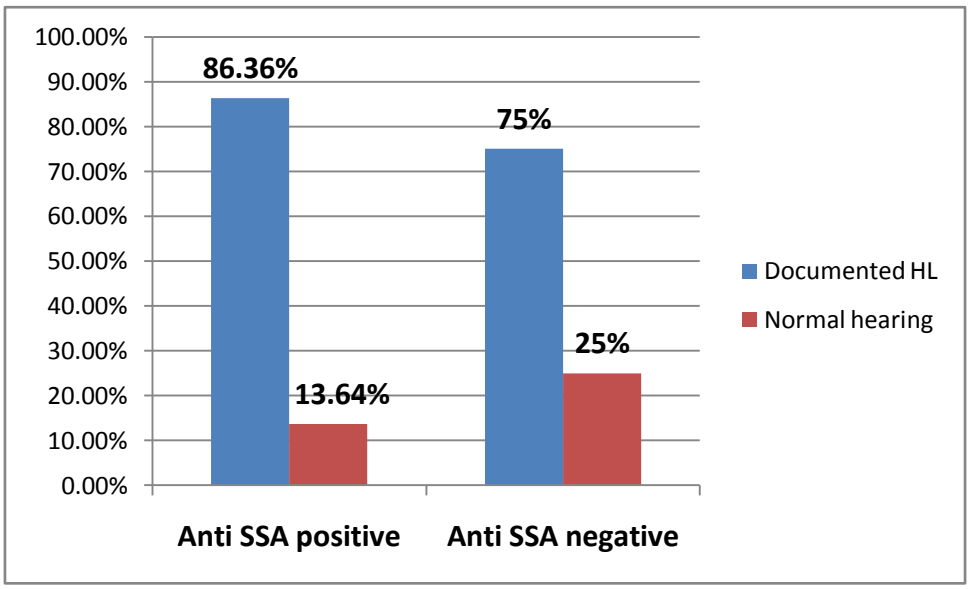
Out of 14 patients with a grade 3 lip biopsy, 13 (92.86%) and only one patient with grade 1 lip biopsy also had a documented hearing loss.

Comparison between hearing loss and anti SS- A positivity is shown in Figure 10.

Out of the 22 patients with positive Anti-SS-A titre, 19 (86.36 %) had documented hearing loss. Out of 12 patients with Negative Anti-SSA titre, 9 (75 %) had documented hearing loss.

Out of the 27 patients with documented hearing loss, 19 ( 70.37 %) had positive anti-SS-A titre. Out of the 7 patients with normal hearing, 4 (57.14%) had positive anti SS-A titre. The difference in hearing loss between those who are positive and negative for anti SS-A was not found to be significantly different. (Chi-sq 0.2208; P value =0.453).

**Figure 10 Comparison between hearing loss and anti SS-A positivity among 37 patients**



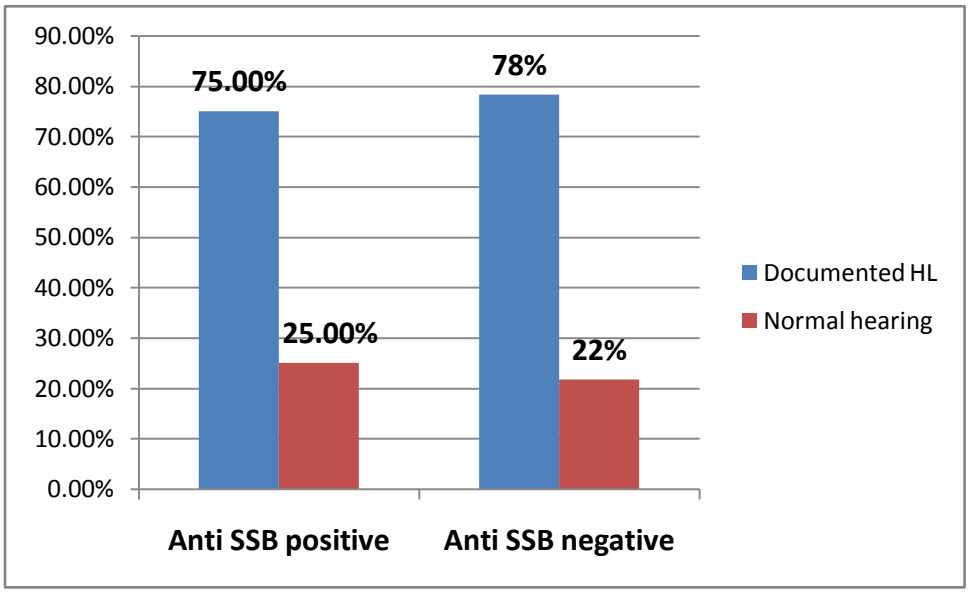
Comparison between hearing loss and anti SS-B positivity is shown in figure 11.

Out of the 12 patients with positive Anti-SSB titre, 9 (75 %) had documented hearing loss.

Out of 23 patients with Negative Anti-SSB titre 18 (78.26 %) had documented hearing loss.

Out of the 27 patients with documented hearing loss, 9 (33.33 %) had positive anti-SSB titre. Out of the 8 patients with normal documented hearing, 3(37.50%) had positive anti SSB titre . The difference in hearing loss between those who are positive and negative for anti SSB was not found to be significantly different (Chi-sq 0.0476; P value =0.827).

**Figure 11 Comparison between hearing loss and anti SS-B positivity among 37 patients**




Out of the 2 patients who had positive anticardiolipin titre, 1(50%) had unilateral minimal sensorineural hearing loss. Out of the 29 patients who had normal anticardiolipin levels, 23(79.31%) had hearing loss. This difference was not statistically significant (Chi sq 1.0522, P value = 0.591).

Out of the 34 patients who had C3 and C4 levels tested only 1 patient had a low C3 and C4 levels, and she had a unilateral SNHL. Two patients had a high C4 level, of these one had unilateral SNHL.

Out of the 33 patients with a normal C3 level, 25(75.76%) had documented hearing loss.

Out of the 30 patients with normal C4 level, 23(76.67%) had documented hearing loss.

Table 9 summarises the sicca symptoms, diagnostic tests done and the pure tone audiogram result of all the 37 patients.

**Table 9: Sicca symptoms, diagnostic tests done and the pure tone audiogram result of 37 patients.**

| S. No | Documented hearing loss | Dry eye | Dry mouth | Schirmer's test | Lip biopsy grade | Anti SS-A | Anti SS-B |
|---|---|---|---|---|---|---|---|
| 1 | Bilateral minimal SNHL | + | + | NA | 4 | + | + |
| 2 | Bilateral minimal SNHL | + | + | NA | 4 | + | - |
| 3 | Bilateral minimal SNHL | + | + | + | 3 | - | - |
| 4 | Bilateral minimal SNHL | + | + | NA | 4 | + | + |
| 5 | Bilateral minimal SNHL | + | + | + | 3 | - | - |
| 6 | Bilateral minimal SNHL | + | + | NA | 4 | + | + |
| 7 | Bilateral minimal SNHL | + | - | + | 4 | + | - |
| 8 | Unilateral minimal SNHL | + | + | + | 4 | NA | NA |
| 9 | Unilateral minimal SNHL | + | + | + | 3 | - | - |
| 10 | Bilateral minimal SNHL | + | + | + | 3 | + | - |
| 11 | Unilateral mild SNHL | + | + | + | 3 | - | - |
| 12 | Unilateral mild SNHL | + | + | + | 1 | + | + |
| 13 | Bilateral minimal SNHL | + | + | NA | 3 | + | + |
| 14 | Bilateral minimal SNHL | + | + | + | 4 | + | + |
| 15 | Bilateral minimal SNHL | + | + | + | 3 | - | - |
| 16 | Bilateral minimal SNHL | + | + | + | NA | + | + |
| 17 | Bilateral minimal SNHL | + | + | NA | 3 | + | - |
| 18 | Unilateral minimal SNHL | + | - | + | 3 | - | - |
| 19 | Normal hearing | + | + | + | NA | + | - |
| 20 | Bilateral minimal SNHL | + | + | + | 4 | + | - |
| 21 | Normal hearing | + | + | + | 4 | - | - |
| 22 | Normal hearing | + | + | + | 4 | + | - |

| S. No | Documented hearing loss | Dry eye | Dry mouth | Schirmer's test | Lip biopsy grade | Anti SS-A | Anti SS-B |
|---|---|---|---|---|---|---|---|
| 23 | Bilateral minimal SNHL | + | + | + | 3 | + | + |
| 24 | Normal hearing | + | + | + | 4 | - | - |
| 25 | Unilateral minimal SNHL | + | + | + | 3 | - | - |
| 26 | Bilateral mild SNHL | + | + | NA | 4 | + | - |
| 27 | Bilateral minimal SNHL | + | + | + | 3 | - | - |
| 28 | Bilateral minimal SNHL | + | + | NA | 4 | + | + |
| 29 | Bilateral minimal SNHL | + | + | + | NA | + | + |
| 30 | Bilateral moderate hearing loss | + | + | + | 3 | - | - |
| 31 | Normal hearing | + | + | + | 3 | - | - |
| 32 | Bilateral minimal SNHL | + | + | + | NA | + | - |
| 33 | Bilateral minimal NSNHL | + | + | NA | 4 | + | - |
| 34 | Bilateral minimal SNHL | + | + | + | NA | + | + |
| 35 | Bilateral mild SNHL | + | + | + | NA | + | - |
| 36 | Normal hearing | + | + | + | NA | + | + |
| 37 | Normal hearing | + | + | + | 4 | + | + |

For sicca symptoms,

**+** = Present; **-** = Absent

For anti SS-A and anti SS-B,

**+** = Positive; **-** = Negative

NA = the test is not done.

# DISCUSSION

In our study, there was a higher rate of recruitment compared to earlier studies from other countries, [Hatzopoulos 2002 / (11), Tumaiti 1997/ (2)]. This perhaps is due to this centre being a large tertiary care centre with a very wide catchment and referral for large parts of the country. The mean age of patients recruited in this study (45 years) was considerably lower than other studies [(55 years), Tumaiti 1997/ (2)]. In keeping with what is known in literature, all but one of the patients in this study were women. The influence of sex hormones on pSS has been discussed in the literature reviewed (10). Androgens have an immune suppressor role, but oestrogens act as immune-stimulants (10).

Duration of illness is a reflection of access to specialist services. In our situation, patients reported within a mean duration of 4.5 years, compared to some other studies reviewed; Ziavara et al (11) 8.3 years, Hatzopoulos et al (10) mean duration of disease for 3 years.

Symptomatically, in comparison with other studies, a large proportion (92%) of our study patients presented with sicca symptoms, 14% with hearing loss and tinnitus. Doig et al (88) , showed marginally fewer with similar symptoms (82% with sicca, 4.5% with hearing loss and tinnitus). Vestibular involvement in patients with pSS is relatively rare; Boki et al (16) did not find significant vestibular involvement while this study had 8% patients with history of vertigo.

Only very few studies have analysed hearing loss in pSS. This study had 78% while other studies, Tumaiti et al (2) reported hearing loss in 46%; Trott et al (9) reported 21.4%, Hatzopoulos (10) 36.3% and Ziavara et al (11) reported hearing loss in 22.5%

patients. SNHL was the commonest hearing loss in this study (97%) and is similar to other studies reviewd. Hatzopoulos (11) reported SNHL in all his patients with hearing loss, Tumaiti et al reported SNHL in all but one patient in their series, as did Ziavara et al (15) in all with hearing loss. While Doig et al were the only study reporting conductive hearing loss in their patients (5 out of 22 patients with hearing loss) . While the suggested cause of conductive hearing loss is dryness of the mucous membranes of the Eustachian tube and middle ear, it should be noted that their study was done before the clear criteria for the diagnosis of the pSS were established by the criteria according to the Modified American European European Classification (81).

There was a predominance of bilateral hearing loss (82.8%) in our study similar to finding in Tumaiti's study (71.43%). Ziavara et al found 44% had bilateral hearing loss and 56% of patients had unilateral hearing loss. This bilaterality may suggest the underlying autoimmune pathology (23).

There is a difference in the severity of SNHL between this study and that of others. In this study, out of 29 with hearing loss, all but one patient had minimal to mild SNHL, classified on the basis of average pure tone threshold for speech frequencies of 500, 1000, and 2000 Hz (88). Tumaiti et al found that out of 15 patients with hearing loss, 9 had minimal hearing loss, 4 had moderate hearing loss and 1 had severe hearing loss and one had mild hearing loss.

In accordance with earlier studies, our study showed hearing loss mainly affects the high frequencies in pSS. It was seen that out of 37 patients, 72.97% patients had a hearing loss affecting high frequencies 4 KHz and 8 KHz. The average threshold for 4 KHz and 8 KHz was 28.56 dB with a maximum of 82.5 dB. Ziavra et al (11) found that

all patients with hearing loss had SNHL affecting mainly the high frequencies. Boki et al (16) had reported significant hearing loss at 4KHz and 8KHz and minimal hearing loss affecting the lower frequencies. Tumaiti et al (2) had found that out of the 14 patients with SNHL, 12 had sloping audiogram involving high frequencies from 2KHz to 4 KHz.

We found no correlation between documented hearing loss and age. This was also reported by Hatzopoulos and Tumaiti in pSS. Ziavara et al (11) concluded that SNHL is found to be associated with disease duration. Tumaiti et al (2) and Hatzopoulos (10) found no statistically significant difference between disease duration between patients with abnormal hearing and those with normal hearing. In contrast to all these previous studies we have observed a different trend of improvement of hearing with the duration of disease. When we assessed the presence of hearing loss in 3 groups divided based on the duration of disease as <1 year, 1-5 years and >5 years, it was observed that as the duration of disease increases, the number of patients with hearing loss decreases. However this difference was not significant (Chi sq = 0.8305 and P value = 0.660) . It may be postulated that this trend may be because of hearing improvement over the course of the disease or because of decreased disease activity due to treatment, which may reflect in the pathogenesis of hearing loss as well. It can also be attributed to the small number of patients in each group we compared. A larger sample size may clarify this suggestion.

The commonest type of tympanogram observed in our study was A type (83.78%). In contrast with the data reported by Hatzopoulos(10) who found that all their 22 patients with pSS had a normal tympanogram, a small proportion (16.22%) of this study had As, Ad, B and C types of curves also. Reflexes were absent in seven patients (18.9%) in contrast to Hatzopoulos whose cases all had reflexes present. Tumaiti et al

found middle-ear pressure to be normal in all their patients and there were no significant differences in mean compliance value between controls and the patients with SS.

Out of the 29 patients in our study, with documented hearing loss, only 5(17.24%) patients complained of a decreased hearing. Rest 24 (82.76%) did not complain of decreased hearing. Tumaiti et al found that 9 of 14 (64.28%) with hearing loss were asymptomatic and they had hearing loss that was detectable only on audiometry.

Diog et al (88) found that among 27% of their patients with hearing loss, none complained of decreased hearing. In our study, there were a higher proportion of asymptomatic hearing loss compared to Tumaiti et al(2). Hearing loss may be the first audiological manifestation of pSS (10). The detection of SNHL in these patients, points to the probability of autoimmune involvement of the ear in this multisystemic autoimmune disease. So it is important to note that hearing evaluation should be made a part of the routine work up of Primary SS patients.

Duration of treatment with HCQ did not significantly change the proportion of patients with hearing loss. This may suggest that HCQ has little adverse effect on hearing in patient with SS.

This study found 65.71% had antibodies to anti SS-A. Tumaiti et al (2) found that 90% of their patients had antibodies to SS-A and it was seen that all patients who had SNHL had antiSS-A positive . Ziavara et al (11) found no correlation between hearing loss and the presence of auto-antibodies. In our study, 86.4 % of patients positive for anti-SSA titre had hearing loss. Presence or absence of hearing loss was not found to be associated with anti SSA positivity in this study. Anti SS-A antibodies are seen in 60-70 percentage of patients with pSS. But these are not specific markers of the disease (38).

Tumaiti et al found 66% patients with antibodies to SS-B. In our study, 75% of patients positive for anti-SSB titre had hearing loss. Presence or absence of hearing loss was not found to be associated with anti SSB positivity in this study. Anti SS-B antibodies are seen in 40-50 percentage of patients with pSS and these are more specific than anti SS-A (38).

Compared to Tumaiti et al study, this study group had a very low proportion with ACA antibodies. ACA is seen in 16% of patients with pSS (41). It was seen that the frequency with which ACA is detected in pSS ranged from 6% to 52% (89,90). Tumaiti et al reported out of 9 (40%) of their patients with positive ACA, 9 (75%) had SNHL (2). They suggested the possible biological association between ACA and SNHL which is suggestive of an underlying autoimmune pathology. In contrary to that we found that hearing loss had no correlation with presence or absence of ACA. Of the 2 patients (6.45%) with positive ACA titre, 1(50%) had SNHL. Ziavara N et al also did not find any correlation between hearing loss and presence of ACA. ACA may be associated with sudden SNHL in patients with autoimmune diseases (25). The one male patient in our study group had all the 3 serological tests anti SS-A, anti SS-B and ACA positive and he had bilateral SNHL.

Tumaiti et al (2) did not find any correlation between hearing loss and C3 and C4 levels as was also seen in our study. The one patient in this study group who had vasculitis and low C3 and C4 level, had unilateral SNHL.

Cryoglobulins are detected in about 20% of patients with pSS (73). But in this study cryoglobulin was not detected in any.

The pathogenesis of immune-mediated SNHL is still not clear. It includes immune complex mediated vasculitis in the inner ear (4) and auto antibodies directed against inner-ear antigenic epitopes (5). The deposition of immune complexes is considered to be the cause for high prevalence of cranial neuropathy in pSS (27,28). The deposition of immune complexes in the stria vascularis or in the endolymphatic sac via complement activation can cause endolymphatic hydrops leading to vestibular symptoms (16,91). This is a preliminary analysis to find the audiological profile of patients with pSS. Further studies are necessary to establish the probable etiologies in this common autoimmune multi-systemic condition.

**Limitations of the study**

Audiological evaluation in pSS patients prior to starting of treatment would have provided more information on the disease process without modification by medication. This is not possible in a tertiary care situation where patients have already been under treatment from other centres for years.

Further audiological evaluation for identifying the site of pathology on the patients detected with hearing loss could not be done due to lack of funds. Such an evaluation would have been helpful in explaining the pathology of the disease process.

It would have been useful to do serial audiological tests to see the progress of hearing loss over time in the same patient. That would have provided a greater insight into the natural history of hearing loss in pSS.

## Conclusions

- The frequency of primary Sjogren's disease is high in this tertiary care rheumatology clinic in this Indian setting.

- The frequency of audiometrically confirmed hearing loss in Primary Sjogren's is 78.38 %.

- The commonest type of hearing loss was minimal to mild sensorineural hearing loss

- The high frequencies were more affected than lower frequencies

- The commonest tympanometry finding was A type curve

- Acoustic reflex was absent in 18.92%

- The frequency of hearing loss was found to be more in the 1$^{st}$ year after onset of SS than after 5 year duration.

- There seems to be no co-relation between hearing loss and age, sicca symptoms, systemic symptoms, immunological test results in primary Sjogren's syndrome

# BIBLIOGRAPHY


1. Soliotis F, Mavragani C, Moutsopoulos H. Central nervous system involvement in Sjögren's syndrome. Ann Rheum Dis. 2004 Jun;63(6):616–20.

2. Tumiati B, Casoli P, Parmeggiani A. Hearing loss in the Sjögren syndrome. Ann. Intern. Med. 1997 Mar 15;126(6):450–3.

3. Steven D.Rauch Michael J.Ruckenstein. Cummings OTOLARYNGOLOGY Head and neck surgery. 5th ed. MOSBY Elsevier;

4. Magaro M, Zoli A, Altomonte L, Mirone L, Corvino G, Di Girolamo S, et al. Sensorineural hearing loss in rheumatoid arthritis. Clin. Exp. Rheumatol. 1990 Oct;8(5):487–90.

5. Elwany S, el Garf A, Kamel T. Hearing and middle ear function in rheumatoid arthritis. J. Rheumatol. 1986 Oct;13(5):878–81.

6. Andonopoulos AP, Naxakis S, Goumas P, Lygatsikas C. Sensorineural hearing disorders in systemic lupus erythematosus. A controlled study. Clin. Exp. Rheumatol. 1995 Apr;13(2):137–41.

7. Gussen P. Polyarteritis nodosa and deafness. A human temporal bone study. Arch Otorhinolaryngol. 1977 Aug 26;217(3):263–71.

8. Kornblut AD, Wolff SM, Fauci AS. Ear disease in patients with Wegener's granulomatosis. Laryngoscope. 1982 Jul;92(7 Pt 1):713–7.

9. Trott MS, Hughes GB, Calabrese LH, Barna BP, Nodar RH. Hearing and Sjögren's syndrome. Ear Nose Throat J. 1996 Oct;75(10):666–8.

10. Hatzopoulos S, Amoroso C, Aimoni C, Lo Monaco A, Govoni M, Martini A. Hearing loss evaluation of Sjögren's syndrome using distortion product otoacoustic emissions. Acta Otolaryngol Suppl. 2002;(548):20–5.

11. Ziavra N, Politi EN, Kastanioudakis I, Skevas A, Drosos AA. Hearing loss in Sjögren's syndrome patients. A comparative study. Clin. Exp. Rheumatol. 2000 Dec;18(6):725–8.

12. Boulassel MR, Deggouj N, Tomasi JP, Gersdorff M. Inner ear autoantibodies and their targets in patients with autoimmune inner ear diseases. Acta Otolaryngol. 2001 Jan;121(1):28–34.

13. Ramos-Casals M, Tzioufas A, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis. 2005 Mar;64(3):347–54.

14. Kassan SS, Moutsopoulos HM. Clinical Manifestations and Early Diagnosis of Sjogren Syndrome. Arch Intern Med. 2004 Jun 28;164(12):1275–84.

15. Fox RI, Stern M, Michelson P. Update in Sjögren syndrome. Curr Opin Rheumatol. 2000 Sep;12(5):391–8.

16. Boki KA, Ioannidis JP, Segas JV, Maragkoudakis PV, Petrou D, Adamopoulos GK, et al. How significant is sensorineural hearing loss in primary Sjögren's syndrome? An individually matched case-control study. J. Rheumatol. 2001 Apr;28(4):798–801.

17. Robinson CP, Yamachika S, Bounous DI, Brayer J, Jonsson R, Holmdahl R, et al. A novel NOD-derived murine model of primary Sjögren's syndrome. Arthritis Rheum. 1998 Jan;41(1):150–6.

18. Boumba D, Skopouli FN, Moutsopoulos HM. Cytokine mRNA expression in the labial salivary gland tissues from patients with primary Sjögren's syndrome. Br. J. Rheumatol. 1995 Apr;34(4):326–33.

19. Tengnér P, Halse AK, Haga HJ, Jonsson R, Wahren-Herlenius M. Detection of anti-Ro/SSA and anti-La/SSB autoantibody-producing cells in salivary glands from patients with Sjögren's syndrome. Arthritis Rheum. 1998 Dec;41(12):2238–48.

20. H.M. M. SjÃ¶c;gren's Syndrome: Autoimmune Epithelitis. Clinical Immunology and Immunopathology. 1994 Aug;72(2):162–5.

21. Abu-Helu RF, Dimitriou ID, Kapsogeorgou EK, Moutsopoulos HM, Manoussakis MN. Induction of salivary gland epithelial cell injury in Sjogren's syndrome: in vitro assessment of T cell-derived cytokines and Fas protein expression. J. Autoimmun. 2001 Sep;17(2):141–53.

22. Dimitriou ID, Kapsogeorgou EK, Moutsopoulos HM, Manoussakis MN. CD40 on salivary gland epithelial cells: high constitutive expression by cultured cells from Sjögren's syndrome patients indicating their intrinsic activation. Clin. Exp. Immunol. 2002 Feb;127(2):386–92.

23. Mc Cabe BF MB. Autoimmune sensorineural hearing loss. Ann Oto Rhino Laryngology. (88):585.

24. LEHNHARDT E. [Sudden hearing disorders occurring simultaneously or successively on both sides]. Z Laryngol Rhinol Otol. 1958 Jan;37(1):1–16.

25. Tumiati B, Casoli P. Sudden sensorineural hearing loss and anticardiolipin antibody. Am J Otolaryngol. 1995 Jun;16(3):220.

26. Alexander EL. Neurologic disease in Sjögren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update of immunopathogenesis. Rheum. Dis. Clin. North Am. 1993 Nov;19(4):869–908.

27. Fox RI, Stern M, Michelson P. Update in Sjögren syndrome. Curr Opin Rheumatol. 2000 Sep;12(5):391–8.

28. Boulassel MR, Tomasi JP, Deggouj N, Gersdorff M. COCH5B2 is a target antigen of anti-inner ear antibodies in autoimmune inner ear diseases. Otol. Neurotol. 2001 Sep;22(5):614–8.

29. Harris JP, Woolf NK, Ryan AF. Elaboration of systemic immunity following inner ear immunization. Am J Otolaryngol. 1985 Jun;6(3):148–52.

30. Harris JP. Immunology of the inner ear: response of the inner ear to antigen challenge. Otolaryngol Head Neck Surg. 1983 Feb;91(1):18–32.

31. Harris JP, Sharp PA. Inner ear autoantibodies in patients with rapidly progressive sensorineural hearing loss. Laryngoscope. 1990 May;100(5):516–24.

32. Nair TS, Prieskorn DM, Miller JM, Mori A, Gray J, Carey TE. In vivo binding and hearing loss after intracochlear infusion of KHRI-3 antibody. Hear. Res. 1997 May;107(1-2):93–101.

33. Nair TS, Kozma KE, Hoefling NL, Kommareddi PK, Ueda Y, Gong T-W, et al. Identification and characterization of choline transporter-like protein 2, an inner ear glycoprotein of 68 and 72 kDa that is the target of antibody-induced hearing loss. J. Neurosci. 2004 Feb 18;24(7):1772–9.

34. McCabe BF. Autoimmune inner ear disease: therapy. Am J Otol. 1989 May;10(3):196–7.

35. Ruckenstein MJ, Sarwar A, Hu L, Shami H, Marion TN. Effects of immunosuppression on the development of cochlear disease in the MRL-Fas(lpr) mouse. Laryngoscope. 1999 Apr;109(4):626–30.

36. Haynes BF, Kaiser-Kupfer MI, Mason P, Fauci AS. Cogan syndrome: studies in thirteen patients, long-term follow-up, and a review of the literature. Medicine (Baltimore). 1980 Nov;59(6):426–41.

37. Gross ND, Kempton JB, Trune DR. Spironolactone blocks glucocorticoid-mediated hearing preservation in autoimmune mice. Laryngoscope. 2002 Feb;112(2):298–303.

38. HM Moutsopoulos. Harrison's Principles of Internal Medicine. 17th edition, chapter 317 ed.

39. Chan EK, Tan EM. Epitopic targets for autoantibodies in systemic lupus erythematosus and Sjögren's syndrome. Curr Opin Rheumatol. 1989 Oct;1(3):376–81.

40. O'Brien CA, Margelot K, Wolin SL. Xenopus Ro ribonucleoproteins: members of an evolutionarily conserved class of cytoplasmic ribonucleoproteins. Proceedings of the National Academy of Sciences. 1993;90(15):7250–4.

41. Ben-Chetrit E, Gandy BJ, Tan EM, Sullivan KF. Isolation and characterization of a cDNA clone encoding the 60-kD component of the human SS-A/Ro ribonucleoprotein autoantigen. J. Clin. Invest. 1989 Apr;83(4):1284–92.

42. Stefano JE. Purified lupus antigen La recognizes an oligouridylate stretch common to the 3' termini of RNA polymerase III transcripts. Cell. 1984 Jan;36(1):145–54.

43. Gottlieb E, Steitz JA. Function of the mammalian La protein: evidence for its action in transcription termination by RNA polymerase III. EMBO J. 1989 Mar;8(3):851–61.

44. Nakamura S, Ikebe-Hiroki A, Shinohara M, Ohyama Y, Mouri T, Sasaki M, et al. An association between salivary gland disease and serological abnormalities in Sjögren's syndrome. J. Oral Pathol. Med. 1997 Oct;26(9):426–30.

45. Gerli R, Muscat C, Giansanti M, Danieli MG, Sciuto M, Gabrielli A, et al. Quantitative assessment of salivary gland inflammatory infiltration in primary Sjögren's syndrome: its relationship to different demographic, clinical and serological features of the disorder. Br. J. Rheumatol. 1997 Sep;36(9):969–75.

46. Manoussakis MN, Tzioufas AG, Pange PJ, Moutsopoulos HM. Serological profiles in subgroups of patients with Sjögren's syndrome. Scand. J. Rheumatol. Suppl. 1986;61:89–92.

47. Alexander EL, Arnett FC, Provost TT, Stevens MB. Sjögren's syndrome: association of anti-Ro(SS-A) antibodies with vasculitis, hematologic abnormalities, and serologic hyperreactivity. Ann. Intern. Med. 1983 Feb;98(2):155–9.

48. Pourmand N, Wahren-Herlenius M, Gunnarsson I, Svenungsson E, Löfström B, Ioannou Y, et al. Ro/SSA and La/SSB specific IgA autoantibodies in serum of patients with Sjögren's syndrome and systemic lupus erythematosus. Ann. Rheum. Dis. 1999 Oct;58(10):623–9.

49. Toker E, Yavuz S, Direskeneli H. Anti-Ro/SSA and anti-La/SSB autoantibodies in the tear fluid of patients with Sjögren's syndrome. Br J Ophthalmol. 2004 Mar;88(3):384–7.

50. Harris EN, Gharavi AE, Boey ML, Patel BM, Mackworth-Young CG, Loizou S, et al. Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. Lancet. 1983 Nov 26;2(8361):1211–4.

51. Hull RG, Harris EN, Gharavi AE, Tincani A, Asherson RA, Valesini G, et al. Anticardiolipin antibodies: occurrence in Behçet's syndrome. Ann Rheum Dis. 1984 Oct;43(5):746–8.

52. Tringali GR, Julian AJ, Halbert WM. Effect of 2-mercaptoethanol treatment on anticardiolipin reactivity in sera from syphilitics and false positive reactors. Br J Vener Dis. 1969 Sep;45(3):202–4.

53. Janeway CA Jr., Travers P, Walport M, Shlomchik MJ, Janeway CA Jr. TP. Immunobiology. 5th ed. Garland Publishing; 2001.

54. Naesens M, Li L, Ying L, Sansanwal P, Sigdel TK, Hsieh S-C, et al. Expression of Complement Components Differs Between Kidney Allografts from Living and Deceased Donors. J Am Soc Nephrol. 2009 Aug;20(8):1839–51.

55. Sacks SH, Chowdhury P, Zhou W. Role of the complement system in rejection. Current Opinion in Immunology. 2003 Oct;15(5):487–92.

56. Moutsopoulos HM. Interview with Haralampos M. Moutsopoulos. What's going to happen as far as the natural history of Sjögren's syndrome is concerned?. Interview by Pierre Youinou. Ann Med Interne (Paris). 1994;145(3):175–6.

57. Ramos-Casals M, Stone JH, Cid MC, Bosch X. The cryoglobulinaemias. The Lancet [Internet]. 2011 Aug [cited 2011 Oct 30];Available from: file:///C:/Users/NIVEDITA/Desktop/New%20folder%20(2)/S0140673611602420.htm

58. Ramos-Casals M, Cervera R, Yagüe J, García-Carrasco M, Trejo O, Jiménez S, et al. Cryoglobulinemia in primary Sjögren's syndrome: prevalence and clinical characteristics in a series of 115 patients. Semin. Arthritis Rheum. 1998 Dec;28(3):200–5.

59. Tzioufas AG, Boumba DS, Skopouli FN, Moutsopoulos HM. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum. 1996 May;39(5):767–72.

60. Pérez B, Kraus A, López G, Cifuentes M, Alarcón-Segovia D. Autoimmune thyroid disease in primary Sjögren's syndrome. Am. J. Med. 1995 Nov;99(5):480–4.

61. Tsokos M, Lazarou SA, Moutsopoulos HM. Vasculitis in primary Sjögren's syndrome. Histologic classification and clinical presentation. Am. J. Clin. Pathol. 1987 Jul;88(1):26–31.

62. Kassan SS. Managing dry eyes and dry mouth in Sjögren's syndrome. Am J Manag Care. 2001 Sep;7(14 Suppl):S444–50.

63. Ostuni P, Botsios C, Sfriso P, Bertagnin A, Cozzi F, Doria A, et al. [Prevalence and clinical features of fibromyalgia in systemic lupus erythematosus, systemic sclerosis and Sjögren's syndrome]. Minerva Med. 2002 Jun;93(3):203–9.

64. Castro-Poltronieri A, Alarcón-Segovia D. Articular manifestations of primary Sjögren's syndrome. J. Rheumatol. 1983 Jun;10(3):485–8.

65. Al-Hashimi I, Khuder S, Haghighat N, Zipp M. Frequency and predictive value of the clinical manifestations in Sjögren's syndrome. J. Oral Pathol. Med. 2001 Jan;30(1):1–6.

66. Franquet T, Díaz C, Domingo P, Giménez A, Geli C. Air trapping in primary Sjögren syndrome: correlation of expiratory CT with pulmonary function tests. J Comput Assist Tomogr. 1999 Apr;23(2):169–73.

67. Ramirez-Mata M, Pena Ancira FF, Alarcon-Segovia D. Abnormal esophageal motility in primary Sjögren's syndrome. J. Rheumatol. 1976 Mar;3(1):63–9.

68. Tsianos EB, Chiras CD, Drosos AA, Moutsopoulos HM. Oesophageal dysfunction in patients with primary Sjögren's syndrome. Ann. Rheum. Dis. 1985 Sep;44(9):610–3.

69. Moutsopoulos HM. Sjögren's syndrome: autoimmune epithelitis. Clin. Immunol. Immunopathol. 1994 Aug;72(2):162–5.

70. Tu WH, Shearn MA, Lee JC, Hopper J Jr. Interstitial nephritis in Sjögren's syndrome. Ann. Intern. Med. 1968 Dec;69(6):1163–70.

71. Shearn MA, Tu W-H. Nephrogenic diabetes insipidus and other defects of renal tubular function in SjÃ¶gren's syndrome. The American Journal of Medicine. 1965 Aug;39(2):312–8.

72. Cohen E, Bastani B, Cohen M, Kolner S, Hemken P, Gluck S. Absence of H(+)-ATPase in cortical collecting tubules of a patient with Sjogren's syndrome and distal renal tubular acidosis. Journal of the American Society of Nephrology. 1992;3(2):264–71.

73. Delalande S, de Seze J, Fauchais A-L, Hachulla E, Stojkovic T, Ferriby D, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore). 2004 Sep;83(5):280–91.

74. Astor FC, Hanft KL, Ciocon JO. Xerostomia: a prevalent condition in the elderly. Ear Nose Throat J. 1999 Jul;78(7):476–9.

75. Ravald N, List T. Caries and periodontal conditions in patients with primary Sjögren's syndrome. Swed Dent J. 1998;22(3):97–103.

76. Scully C. Sjögren's syndrome: clinical and laboratory features, immunopathogenesis, and management. Oral Surg. Oral Med. Oral Pathol. 1986 Nov;62(5):510–23.

77. Fox PC, Atkinson JC, Macynski AA, Wolff A, Kung DS, Valdez IH, et al. Pilocarpine Treatment of Salivary Gland Hypofunction and Dry Mouth (Xerostomia). Arch Intern Med. 1991 Jun 1;151(6):1149–52.

78. MacKay BJ, Denepitiya L, Iacono VJ, Krost SB, Pollock JJ. Growth-inhibitory and bactericidal effects of human parotid salivary histidine-rich polypeptides on Streptococcus mutans. Infection and Immunity. 1984 Jun 1;44(3):695–701.

79. Main BE, Calman KC, Ferguson MM, Kaye SB, MacFarlane TW, Mairs RJ, et al. The effect of cytotoxic therapy on saliva and oral flora. Oral Surg. Oral Med. Oral Pathol. 1984 Nov;58(5):545–8.

80. Epstein JB, Truelove EL, Izutzu KT. Oral candidiasis: pathogenesis and host defense. Rev. Infect. Dis. 1984 Feb;6(1):96–106.

81. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann. Rheum. Dis. 2002 Jun;61(6):554–8.

82. Tzioufas AG, Boumba DS, Skopouli FN, Moutsopoulos HM. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predictive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum. 1996 May;39(5):767–72.

83. Friedmann. Scott-Brown's Otolaryngology. 6th ed. 1-50 p.

84. A Fitzgerald O'Connor. Scott-Brown's Otolaryngology. 6th ed. 1-29 p.

85. Jack Katz RFB. Handbook of clinical audiology. 5th ed. Lippincott Williams & Wilkins; 71-87 p.

86. Robert F.Burkard JK. Handbook of clinical audiology. 5th ed. Lippincott Williams & Wilkins; 175-202 p.

87. Alan G.Kerr AW. Scott-Brown's Otolaryngology. 6th ed. 1/1/1- 1/1/50 p.

88. Doig JA, Whaley K, Dick WC, Nuki G, Williamson J, Buchanan WW. Otolaryngological aspects of Sjögren's syndrome. Br Med J. 1971 Nov 20;4(5785):460–3.

89. Manoussakis MN, Gharavi AE, Drosos AA, Kitridou RC, Moutsopoulos HM. Anticardiolipin antibodies in unselected autoimmune rheumatic disease patients. Clin. Immunol. Immunopathol. 1987 Sep;44(3):297–307.

90. Buchanan RR, Wardlaw JR, Riglar AG, Littlejohn GO, Miller MH. Antiphospholipid antibodies in the connective tissue diseases: their relation to the antiphospholipid syndrome and forme fruste disease. J. Rheumatol. 1989 Jun;16(6):757–61.

91. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum. 1993 Mar;36(3):340–7.

# APPENDIX 1

## Patient Information sheet

**Study Title**- Audiological profile of patients with confirmed diagnosis of Sjogren's Syndrome (SS) in an Indian setting.

SS is an immune disease affecting mainly some of the glands in the body. Studies in the western countries have shown that hearing is affected in about 40 to 50 percent of patients with this disease. It is more common in women than in men. There are no studies done in Indian population about the hearing problems in patients who have SS.

The Rheumatology and Audio vestibular Units are conducting a study to see the extend of hearing problems in Indian patients with SS.

**What do you have to do?**

You will be asked to answer a questionnaire and undergo a detail Ear, Nose and Throat examination. Then you will have to do two tests - Pure Tone Audiometry and Impedance Audiometry are painless and cause no discomfort.

Pure Tone Audiometry-This is a simple, non invasive, painless test to determine the type and degree of hearing loss using an electronic device called Audiometer.

Impedance Audiometry-This is a simple, non-invasive, painless test to find out the health status of middle ear using an ear probe with 3 channels.

All these tests are routine and will not result in any extra cost or harm you in any way.

The benefit of this study to you is that if you complain of hearing loss, it can be evaluated and treated accordingly and if you do not complain of hearing loss, early hearing loss can be diagnosed and measures can be taken to prevent worsening of hearing.

Your participation in the study is voluntary and you are free to withdraw at any time, without giving any reason. As the study doesn't include any trial treatment, there is no extra risk for you due to your participation in the study. There is absolutely no additional cost to you as a result of participation in this study.

If you are willing to participate in this study, you will be required to sign in the following consent form.

***Contact Person***

Dr. Thanooja CV
Dept of ENT,
CMC Vellore

# APPENDIX 2

**Informed Consent form to participate in an observational study**

**Study Title-** Audiological profile of patients with confirmed diagnosis of Sjogrens Syndrome (SS) in an Indian setting.

**Study Number:**

**Subject's Initials:**

**Subject's Name:**

**Date of Birth / Age:**

Please put your signature here

**(Subject)**

i. I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.

ii. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

iii. I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

iv. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

v. I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Date:

Signatory's Name: _____

Signature of the Investigator: _____

Date: Study Investigator's Name: _____

Signature of the Witness: _____

Date:

Name of the Witness: _____

# Appendix 3

## PROFORMA

Audiological profile in Sjogren's syndrome in an Indian setting

Serial Number :

Name :

Age

Sex : Hospital number :

Occupation : Contact number :

Address: email Id:

Date of interview-

Symptoms present at onset

Dry eye- Foreign body sensation eye-

Dry mouth- Persistent salivary gland swelling-

Duration since onset of first symptom of Sjogrens syndrome-

History of hearing loss –Yes/No

Rt/ Lt/ B/L

If yes duration-

Sudden/ Progressive/ Gradually progressive

History of tinnitus - Yes/No

Rt/ Lt/ B/L

If yes duration-

History of vertigo-Yes/No

If yes duration-

Any other ear symptoms-

Drugs -Chloroquine Yes/ No duration-

Methotrexate - Yes/ No duration-

Other drugs-

Any other medical conditions present-(HT/DM/Hypothyroidism/Dyslipidaemia)

If yes on treatment?-Yes/No

Any family history of similar complaint?i.e.Sjogrens syndrome/other autoimmune conditions?-

EXAMINATION

Ear-

Nose and throat if any symptoms present-

Neuro ontological examination if indicated-

INVESTIGATIONS

Pre morbid audiogram- Yes/ No

| Pure Tone Audiogram- | Rt (AC/BC) | Lt(AC/BC) |
|---|---|---|
| 250 | | |
| 500 | | |
| 1000 | | |
| 2000 | | |
| 4000 | | |
| 8000 | | |

| Current Audiogram - (date) | Rt(AC/BC) | Lt(AC/BC) |
|---|---|---|
| 250 | | |
| 500 | | |
| 1000 | | |
| 2000 | | |
| 4000 | | |
| 8000 | | |

Impedance

| Tympanogram (date) | Rt | Lt |
|---|---|---|
| Type of curve | | |
| Volume | | |
| Reflex | *Present/Absent* | *Present/Absent* |

Serological parameters

C3

C4

Cryoglobulin

SSA

SSB

Anticardiolipin

# Colour plates

**Figure 12: Audio meter**


**Figure 13: Tympano meter**

**Figure 14: Pure Tone Audiometry**


**Figure 15: Tympanometry**

# MASTER SHEET

| SerilNo | Name | Age | Sex | HospNo | DryEye | EyeDurn | Schirmer | DryMouth | MouthDur | LipBx | FBSenEye | FBsenDu | salivgla | SalivDur | Others | OthrDurn | Durlsym | HearLoss | HLDurn | Onset | HLSide | Tinnitus | TinnDurn | side | Vertigo | VertDurn | DurtnRx | HCQ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ashrukana Das | 61 | 1 | 739724d | 1 | 12 | 3 | 1 | 12 | 4 | 1 | 12 | 0 | 0 | 2 | 18 | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 |
| 2 | Sovamal paharia | 47 | 1 | 459368c | 1 | 120 | 3 | 1 | 120 | 4 | 1 | 60 | 0 | 0 | 1 | 120 | 120 | 1 | 24 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 3 | Kokila | 55 | 1 | 065781d | 1 | 48 | 1 | 1 | 48 | 3 | 0 | 0 | 0 | 0 | 1 | 120 | 120 | 0 | 0 | 0 | 0 | 1 | 60 | 1 | 0 | 0 | 36 | 1 |
| 4 | Padmavathy.P | 28 | 1 | 747872d | 1 | 6 | 3 | 1 | 6 | 4 | 1 | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 1 |
| 5 | Vinita srivastava | 38 | 1 | 196869d | 1 | 24 | 1 | 1 | 24 | 3 | 0 | 0 | 0 | 0 | 1 | 48 | 48 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 1 |
| 6 | Muthusami K | 37 | 2 | 363755d | 1 | 120 | 3 | 1 | 120 | 4 | 1 | 12 | 0 | 0 | 0 | 0 | 120 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 1 |
| 7 | Minati saha | 45 | 1 | 660043d | 1 | 12 | 1 | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 | 1 |
| 8 | Lalitha | 40 | 1 | 674455a | 1 | 48 | 3 | 1 | 48 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 48 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 9 | Urmila | 43 | 1 | 390697d | 0 | 0 | 1 | 1 | 24 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 1 |
| 10 | Suparna Ray | 37 | 1 | 741102d | 1 | 48 | 1 | 1 | 24 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 48 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 |
| 11 | Vanithamani | 55 | 1 | 085203c | 1 | 6 | 1 | 1 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 72 | 6 | 1 |
| 12 | Dr.Bhagyalakshmi | 53 | 1 | 970995d | 1 | 48 | 1 | 1 | 48 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 48 | 1 | 48 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | Susila Devi | 60 | 1 | 925569d | 1 | 180 | 3 | 1 | 180 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 180 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 |
| 13 | Valliyammal | 55 | 1 | 894487d | 1 | 36 | 1 | 1 | 36 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 0 | 0 | 0 | 0 | 1 | 24 | 2 | 0 | 0 | 36 | 1 |
| 15 | Angeline Jwbaseline | 62 | 1 | 957591d | 1 | 7 | 1 | 1 | 12 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | Regina | 50 | 1 | 163142a | 1 | 1 | 1 | 1 | 54 | 0 | 1 | 48 | 1 | 48 | 0 | 0 | 54 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 6 | 48 | 1 |
| 17 | Bineeta kumari | 35 | 1 | 502844d | 1 | 24 | 3 | 1 | 24 | 3 | 0 | 0 | 0 | 0 | 1 | 24 | 24 | 0 | 0 | 0 | 0 | 1 | 7 | 3 | 0 | 0 | 18 | 1 |
| 18 | Shipra saha | 38 | 1 | 684959c | 1 | 12 | 1 | 0 | 0 | 3 | 1 | 12 | 0 | 0 | 0 | 0 | 12 | 1 | 12 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 12 | 1 |
| 19 | Santhi | 40 | 1 | 902681d | 1 | 12 | 1 | 1 | 12 | 0 | 0 | 0 | 0 | 0 | 1 | 24 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 |
| 20 | Jeeva | 37 | 1 | 029338b | 1 | 3 | 1 | 1 | 3 | 4 | 0 | 0 | 1 | 3 | 1 | 48 | 48 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 |
| 21 | Arati das | 53 | 1 | 750635d | 1 | 60 | 1 | 1 | 60 | 4 | 0 | 0 | 0 | 0 | 1 | 120 | 120 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 84 | 1 |
| 22 | Pushpavathy | 43 | 1 | 872526d | 1 | 12 | 1 | 1 | 12 | 4 | 0 | 0 | 0 | 0 | 1 | 12 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 |
| 23 | Kalpana | 26 | 1 | 628271d | 1 | 24 | 1 | 1 | 24 | 3 | 0 | 0 | 0 | 0 | 1 | 24 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 24 | Shakila | 50 | 1 | 094937d | 0 | 0 | 1 | 0 | 0 | 4 | 1 | 12 | 0 | 0 | 1 | 84 | 84 | 0 | 0 | 0 | 0 | 1 | 12 | 1 | 0 | 0 | 24 | 0 |
| 25 | Sree mathini | 61 | 1 | 1066126a | 1 | 72 | 1 | 1 | 72 | 3 | 0 | 0 | 0 | 0 | 1 | 48 | 72 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 60 | 1 |
| 26 | Pratima | 38 | 1 | 947537d | 1 | 12 | 3 | 1 | 12 | 4 | 1 | 12 | 0 | 0 | 1 | 96 | 96 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 1 |
| 27 | Sujatha | 33 | 1 | 835030b | 1 | 7 | 1 | 1 | 6 | 3 | 1 | 7 | 0 | 0 | 1 | 7 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 1 |
| 28 | Punam devi | 46 | 1 | 566756d | 1 | 24 | 3 | 1 | 24 | 4 | 1 | 24 | 0 | 0 | 1 | 120 | 120 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 29 | Punithavathy | 63 | 1 | 412449 | 1 | 24 | 1 | 1 | 24 | 0 | 1 | 24 | 0 | 0 | 1 | 180 | 180 | 1 | 12 | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 30 | Girijasathya | 48 | 1 | 386513a | 1 | 36 | 1 | 1 | 36 | 3 | 1 | 36 | 0 | 0 | 1 | 42 | 42 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 1 |
| 31 | Parvathy Devi | 36 | 1 | 682948d | 1 | 36 | 1 | 1 | 36 | 3 | 1 | 36 | 0 | 0 | 1 | 36 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 24 | 1 |
| 32 | Mohana | 53 | 1 | 886316c | 1 | 72 | 1 | 1 | 72 | 0 | 1 | 72 | 0 | 0 | 1 | 72 | 72 | 1 | 12 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 60 | 1 |
| 33 | Mohini J | 42 | 1 | 059637f | 1 | 6 | 0 | 1 | 6 | 4 | 1 | 6 | 0 | 0 | 0 | 0 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 1 |
| 34 | Gangabai | 51 | 1 | 672117d | 1 | 12 | 1 | 1 | 12 | 0 | 1 | 12 | 0 | 0 | 0 | 0 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 |
| 35 | Imbavally | 55 | 1 | 1905756d | 1 | 24 | 1 | 1 | 24 | 0 | 1 | 24 | 0 | 0 | 2 | 24 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 1 |
| 36 | Nallammal | 53 | 1 | 167370d | 1 | 60 | 1 | 1 | 60 | 0 | 1 | 60 | 0 | 0 | 0 | 0 | 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 | 1 |
| 37 | Roshan Ara | 28 | 1 | 846852d | 1 | 24 | 1 | 1 | 24 | 4 | 1 | 24 | 1 | 2 | 0 | 0 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 12 | 6 | 1 |

| SerilNo | HCQdurn | MTX | MTXDurn | HT | Htdurn | HYPOTHYR | Hypodurn | DM | DMdurn | DYSLIPID | Dyslidur | 250RtAC | 250RtBC | 250LtAC | 250LtBC | 500RtAC | 500RtBC | 500LtAC | 500LtBC | 1KRtAC | 1kRtBC | 1KLtAC | 1KLtBC | 2KRtAC | 2KRtBC | 2KLtAC | 2KLtBC | 4KRtAC | 4KRtBC | 4KLtAC | 4KLtBC | 8KRtAC | 8kLtAC | Highfreq | Avg4k8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 30 | 1 | 25 |
| 2 | 24 | 1 | 8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 20 | 40 | 30 | 40 | 35 | 1 | 35 |
| 3 | 36 | 1 | 36 | 1 | 120 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 10 | 10 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 30 | 1 | 25 |
| 4 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 25 | 20 | 0 | 22.5 |
| 5 | 36 | 1 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 10 | 10 | 10 | 10 | 20 | 20 | 20 | 20 | 30 | 30 | 1 | 25 |
| 6 | 12 | 1 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 20 | 20 | 25 | 25 | 20 | 20 | 25 | 25 | 25 | 25 | 20 | 20 | 20 | 20 | 35 | 35 | 35 | 35 | 40 | 40 | 1 | 37.5 |
| 7 | 9 | 0 | 0 | 1 | 60 | 1 | 36 | 0 | 0 | 0 | 0 | 20 | 20 | 15 | 15 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 30 | 30 | 15 | 15 | 50 | 30 | 1 | 40 |
| 8 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 15 | 15 | 20 | 20 | 15 | 15 | 15 | 15 | 10 | 10 | 20 | 20 | 20 | 20 | 15 | 15 | 40 | 40 | 40 | 35 | 1 | 27.5 |
| 9 | 36 | 0 | 0 | 1 | 180 | 1 | 180 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 15 | 15 | 20 | 20 | 20 | 20 | 20 | 25 | 1 | 20 |
| 10 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 20 | 20 | 1 | 20 |
| 11 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 40 | 10 | 70 | 0 | 35 | 10 | 70 | 0 | 25 | 15 | 55 | 0 | 30 | 30 | 60 | 35 | 25 | 25 | 55 | 30 | 45 | 55 | 1 | 35 |
| 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 40 | 40 | 20 | 20 | 35 | 35 | 15 | 15 | 25 | 25 | 15 | 15 | 25 | 25 | 15 | 15 | 20 | 20 | 20 | 30 | 1 | 17.5 |
| 13 | 2 | 0 | 0 | 0 | 0 | 1 | 180 | 0 | 0 | 0 | 0 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 30 | 30 | 30 | 30 | 30 | 40 | 1 | 30 |
| 13 | 36 | 0 | 0 | 0 | 0 | 1 | 96 | 0 | 0 | 0 | 0 | 15 | 15 | 10 | 10 | 15 | 15 | 10 | 10 | 15 | 15 | 10 | 10 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 20 | 20 | 1 | 25 |
| 15 | 0 | 0 | 0 | 0 | 0 | 1 | 36 | 0 | 0 | 0 | 0 | 20 | 20 | 30 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 15 | 15 | 20 | 20 | 20 | 20 | 30 | 20 | 0 | 25 |
| 16 | 48 | 0 | 0 | 1 | 96 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 15 | 15 | 20 | 20 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 15 | 15 | 35 | 35 | 1 | 27.5 |
| 17 | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 1 | 20 |
| 18 | 12 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 48 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 10 | 10 | 15 | 15 | 20 | 20 | 20 | 20 | 30 | 30 | 20 | 20 | 15 | 10 | 0 | 22.5 |
| 19 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 20 | 20 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 10 | 10 | 35 | 35 | 1 | 25 |
| 20 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 15 | 15 | 20 | 15 | 0 | 20 |
| 21 | 84 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 15 | 15 | 15 | 15 | 10 | 10 | 15 | 15 | 30 | 30 | 30 | 30 | 20 | 20 | 1 | 25 |
| 22 | 6 | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 10 | 10 | 40 | 40 | 35 | 35 | 20 | 20 | 1 | 30 |
| 23 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 20 | 20 | 30 | 30 | 20 | 40 | 1 | 20 |
| 24 | 0 | 1 | 24 | 1 | 24 | 1 | 24 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 20 | 20 | 10 | 10 | 10 | 10 | 15 | 15 | 15 | 15 | 10 | 10 | 25 | 15 | 0 | 20 |
| 25 | 60 | 0 | 0 | 1 | 72 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 10 | 15 | 15 | 10 | 10 | 20 | 20 | 10 | 10 | 20 | 20 | 10 | 10 | 15 | 15 | 10 | 10 | 15 | 15 | 10 | 15 | 0 | 10 |
| 26 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 30 | 30 | 30 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 0 | 20 |
| 27 | 7 | 1 | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 0 | 15 |
| 28 | 24 | 1 | 24 | 0 | 0 | 1 | 120 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 10 | 10 | 20 | 20 | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 | 5 | 5 | 15 | 5 | 0 | 12.5 |
| 29 | 24 | 1 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 35 | 20 | 20 | 20 | 30 | 30 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 20 | 15 | 15 | 20 | 25 | 1 | 25 |
| 30 | 36 | 1 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 0 | 40 | 10 | 20 | 10 | 45 | 20 | 25 | 15 | 45 | 20 | 50 | 40 | 50 | 40 | 60 | 50 | 80 | 50 | 100 | 90 | 1 | 80 |
| 31 | 24 | 1 | 24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 15 | 15 | 10 | 10 | 25 | 25 | 1 | 20 |
| 32 | 60 | 1 | 60 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 40 | 1 | 25 |
| 33 | 5 | 1 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 20 | 20 | 20 | 45 | 55 | 1 | 37.5 |
| 34 | 6 | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 30 | 20 | 30 | 20 | 35 | 35 | 1 | 32.5 |
| 35 | 6 | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 20 | 10 | 20 | 10 | 20 | 10 | 25 | 15 | 30 | 30 | 20 | 20 | 35 | 35 | 30 | 30 | 50 | 40 | 20 | 20 | 90 | 30 | 1 | 35 |
| 36 | 36 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 20 | 20 | 40 | 20 | 1 | 27.5 |
| 37 | 6 | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 10 | 10 | 10 | 10 | 10 | 10 | 15 | 15 | 10 | 10 | 10 | 10 | 15 | 15 | 0 | 12.5 |

| SerilNo | Avg4k8Lt | HLPTA | HL | ImpRt | ImpLt | ReflxRt | ReflxLt | C3 | C3Range | C4 | C4Range | Cryoglob | SSA | SSArange | SSB | SSBrange | Anticard | Antirang |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 25 | 2 | 1 | 1 | 1 | 1 | 1 | 131 | 2 | 20.9 | 2 | 0 | 192 | 1 | 20 | 1 | 2 | 0 |
| 2 | 37.5 | 2 | 1 | 1 | 1 | 1 | 1 | 98.6 | 2 | 31.5 | 2 | 0 | 200.6 | 1 | 1 | 0 | 5 | 0 |
| 3 | 25 | 2 | 1 | 1 | 1 | 1 | 1 | 148 | 2 | 27.1 | 2 | 0 | 1 | 0 | 1 | 0 | 2 | 0 |
| 4 | 20 | 2 | 1 | 1 | 1 | 1 | 1 | 99.3 | 2 | 30.5 | 2 | 0 | 179 | 1 | 89 | 1 | 2 | 0 |
| 5 | 25 | 2 | 1 | 1 | 2 | 1 | 1 | 103 | 2 | 20.5 | 2 | 0 | 1 | 0 | 1 | 0 | 2 | 0 |
| 6 | 37.5 | 2 | 1 | 1 | 1 | 1 | 1 | 93.4 | 2 | 18.8 | 2 | 0 | 212 | 1 | 190 | 1 | 31 | 1 |
| 7 | 22.5 | 2 | 1 | 1 | 1 | 1 | 1 | 139 | 2 | 43.8 | 3 | 0 | 40 | 1 | 2 | 0 | 2 | 0 |
| 8 | 37.5 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 3 | 0 | 3 |
| 9 | 22.5 | 1 | 1 | 1 | 1 | 1 | 1 | 113 | 2 | 39.6 | 2 | 0 | 6 | 0 | 4 | 0 | 2 | 0 |
| 10 | 20 | 2 | 1 | 2 | 2 | 1 | 1 | 54.5 | 1 | 9.74 | 1 | 0 | 217 | 1 | 9 | 0 | 3 | 0 |
| 11 | 55 | 3 | 1 | 1 | 2 | 0 | 0 | 163 | 2 | 28 | 2 | 0 | 1 | 0 | 1 | 0 | 6 | 0 |
| 12 | 25 | 7 | 1 | 1 | 1 | 1 | 1 | 113 | 2 | 29.6 | 2 | 0 | 119 | 1 | 262 | 1 | 4 | 0 |
| 13 | 35 | 2 | 1 | 1 | 1 | 1 | 1 | 138 | 2 | 35.2 | 2 | 0 | 110 | 1 | 319 | 1 | 0 | 3 |
| 13 | 25 | 2 | 1 | 1 | 1 | 1 | 1 | 101 | 2 | 13.6 | 2 | 0 | 214 | 1 | 248 | 1 | 3 | 0 |
| 15 | 20 | 2 | 1 | 1 | 1 | 1 | 1 | 107 | 2 | 14.7 | 2 | 0 | 2 | 0 | 1 | 0 | 6 | 0 |
| 16 | 25 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 | 3 |
| 17 | 25 | 2 | 1 | 1 | 1 | 1 | 1 | 165 | 2 | 29.9 | 2 | 0 | 249 | 1 | 0 | 0 | 6 | 0 |
| 18 | 15 | 1 | 1 | 3 | 1 | 0 | 1 | 103 | 2 | 34.7 | 2 | 0 | 1 | 0 | 1 | 0 | 3 | 0 |
| 19 | 25 | 0 | 0 | 1 | 1 | 1 | 1 | 123 | 2 | 25.3 | 2 | 3 | 192 | 1 | 1 | 0 | 3 | 0 |
| 20 | 15 | 2 | 1 | 1 | 1 | 1 | 1 | 122 | 2 | 18 | 2 | 0 | 65 | 1 | 2 | 0 | 3 | 0 |
| 21 | 25 | 0 | 0 | 1 | 1 | 0 | 0 | 118 | 2 | 20.6 | 2 | 0 | 2 | 0 | 1 | 0 | 0 | 3 |
| 22 | 27.5 | 0 | 0 | 1 | 1 | 1 | 1 | 150 | 2 | 22.6 | 2 | 0 | 153 | 1 | 4 | 0 | 2 | 0 |
| 23 | 35 | 2 | 1 | 5 | 1 | 0 | 0 | 120 | 2 | 23.9 | 2 | 0 | 189 | 1 | 265 | 1 | 4 | 0 |
| 24 | 12.5 | 0 | 0 | 1 | 1 | 1 | 1 | 142 | 2 | 38.6 | 2 | 0 | 1 | 0 | 1 | 0 | 3 | 0 |
| 25 | 15 | 1 | 1 | 3 | 5 | 1 | 1 | 121 | 2 | 31.8 | 2 | 0 | 1 | 0 | 1 | 0 | 2 | 0 |
| 26 | 20 | 4 | 1 | 1 | 1 | 1 | 1 | 113 | 2 | 21.5 | 2 | 0 | 50 | 1 | 3 | 0 | 4 | 0 |
| 27 | 17.5 | 2 | 1 | 1 | 1 | 1 | 1 | 162 | 2 | 25.8 | 2 | 3 | 1 | 0 | 1 | 0 | 3 | 0 |
| 28 | 5 | 0 | 0 | 1 | 1 | 1 | 1 | 103 | 2 | 17.4 | 2 | 0 | 123 | 1 | 176 | 1 | 1 | 0 |
| 29 | 20 | 2 | 1 | 1 | 1 | 1 | 1 | 126 | 2 | 39.7 | 2 | 3 | 200 | 1 | 257 | 1 | 4 | 0 |
| 30 | 85 | 8 | 1 | 1 | 4 | 0 | 0 | 164 | 2 | 43.4 | 3 | 0 | 1 | 0 | 1 | 0 | 2 | 0 |
| 31 | 20 | 0 | 0 | 1 | 1 | 1 | 1 | 161 | 2 | 41.3 | 3 | 3 | 1 | 0 | 1 | 0 | 5 | 0 |
| 32 | 30 | 2 | 1 | 1 | 1 | 1 | 1 | 124 | 2 | 24.1 | 2 | 3 | 76 | 1 | 3 | 0 | 1 | 0 |
| 33 | 37.5 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 67 | 1 | 2 | 0 | 0 | 0 |
| 34 | 32.5 | 2 | 1 | 2 | 4 | 0 | 0 | 122 | 2 | 10.7 | 2 | 0 | 215 | 1 | 159 | 1 | 0 | 3 |
| 35 | 25 | 4 | 1 | 3 | 1 | 1 | 1 | 130 | 2 | 24.3 | 2 | 0 | 167 | 1 | 18 | 0 | 0 | 3 |
| 36 | 20 | 0 | 0 | 1 | 1 | 1 | 1 | 103 | 2 | 24.7 | 2 | 3 | 191 | 1 | 222 | 1 | 21 | 1 |
| 37 | 12.5 | 0 | 0 | 1 | 1 | 1 | 1 | 137 | 2 | 24.1 | 2 | 0 | 216 | 1 | 268 | 1 | 2 | 0 |